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THE HISTORY OF MIDDLESEX NORTH DISTRICT MEDICAL SOCIETY 1844–1944*

ARCHIBALD R. GARDNER, M.D.
LOWELL, MASSACHUSETTS

CONDENSATION of time and space is one of the important characteristics of this civilization, and, as this is the centennial anniversary of our local society, an attempt will be made to condense one hundred years of its growth within the short time allotted. The great historian Livy complained of the scant records of the early history of Rome, but that was not my difficulty in this case. My problem was to select from the abundance of records some topics that might be of interest to you. Most of us like people better than dates, which is indeed an essential trait of physicians. There are, however, a few dates and associations of our early society's chronicles that will give a historical perspective.

No discourse pertaining to the history of the Middlesex North District Medical Society should be given without a clear statement of its relation to its parent, the Massachusetts Medical Society. The latter, founded one hundred and sixty-three years ago, is the oldest medical society in the United States with a record of uninterrupted activities from its founding to the present time.

In the Charter Act of the Legislature of 1781, there was no provision for the forming of local or district medical societies, integral parts of the parent society, in the different sections of the Commonwealth. These district or county medical societies have since become prominent features of all state medical societies, their boundaries usually conforming to counties.

In 1829 the first medical association in Middlesex County was formed. The meeting was held in Lexington. Dr. Josiah Bartlett, of Chelmsford, was chosen president, and Dr. F. S. Hurd secretary. The physicians of Lowell who were present at that meeting were Drs. Green, Huntington, Crosby and Bartlett. Unfortunately, the records of this association have been lost.

In 1833 the members were forced to dissolve their association on account of the time and expense involved in going by stage to and from their then distant places of meeting, and for several years there was no formal organization or association of physicians in this vicinity.

The town of Lowell was rapidly growing, following the building of its fine system of canals, which so greatly contributed to the ever increasing textile industry. By 1836 the town had become a city. Keeping pace with this growth, the number of physicians was increasing, and the old association had awakened a spirit, for in man there is an instinct to band with others for mutual benefit, not alone in matters of government, but also for the help derived from aggregate knowledge and experience, this being especially true regarding the followers of our calling. So it was but natural that another medical association should be formed.

In 1839, a special meeting of Lowell physicians was held at the office of Dr. J. D. Pillsbury to organize a society for mutual improvement, at which time the Lowell Medical Association was formed. The following physicians were present: Elisha Bartlett, John C. Dalton, James W. Ford, J. W. Graves, William Grey, J. P. Jewett, Gilman Kimball, George Mansfield, Daniel Mowe, Hiram Parker, Otis Perham, Harlin Pillsbury, J. D. Pillsbury, J. W. Scribner, Benjamin Skelton and Daniel Wells. This voluntary association of high character continued to grow in numbers and increase in interest until at the end of five years a request was made by some members of the Massachusetts Medical Society, resident in this vicinity, for the establishment of a district medical society.

The committee reported at the October meeting in that year that they had drawn up a petition for such a society, which had been signed by twenty-three out of twenty-seven fellows residing in the proposed district, and accordingly recommended that a charter be granted. This was passed promptly by a unanimous vote. The petition follows.

> The undersigned members of the Massachusetts Medical Society, resident in the northerly section of the County of Middlesex, believe that the establishment of a district medical society within its limits embracing the following towns namely: Lowell, Billerica, Ashby, Townsend, Pepperell, Dunstable, Groton, Shirley, Tyngsboro, Chelmsford, Carlisle, Littleton, Dracut, Tewksbury, Concord, and Acton (the meetings of which shall be holden in the City

*An address delivered at the Centennial Observance of the Middlesex North District Society, December 6, 1944.

of Lowell) would be of great utility. Being desirous of enjoying the advantages and privileges of such an institution, we do hereby pledge ourselves (should a petition for a charter to that effect already in the hands of the Councillors be granted) to become active members of the same, by attending its meetings and otherwise promoting the interest as opportunity may occur.

This charter was received November 2, 1844, and the society was known as the Middlesex District Medical Society.

In 1850 a slight change was made. Middlesex County was divided into three districts — east, north and south. This city and eighteen neighboring towns were included in the North District, and the name of the society was changed to the Middlesex North District Medical Society, which it has retained ever since. The caliber of the members in the society of that period can be judged from the fact that in their desire to perpetuate their knowledge of medical science Dr. Elisha Huntington petitioned the Legislature for a charter to establish a medical school in Lowell.

In the formation of medical societies at that time, the objects were to combine physicians and surgeons duly qualified to serve the public as such, to point out the education to be pursued by those who should be desirous of entering our profession, to examine persons who had pursued this course and to give licenses to such as should be found qualified to engage in practice.

The medical societies in those years were the only organizations that controlled the standards of medical practice. It was not until 1894 that Massachusetts joined the majority of the other states of the Union in adopting a medical practice act, thereby establishing the Board of Registration in Medicine. This act, indeed, proved most undesirable, since it allowed incompetent doctors to be registered in the Commonwealth, but after years of constant efforts on the part of the medical societies, the Legislature was lately induced to correct conditions by passing a satisfactory bill. One has only to read the various advertisements in the magazines and journals of those days to note the extent of quackery and charlatanism. It has been stated that with the promotion of the local district medical society, the public in this locality had its first effective protection from those unscrupulous and dishonest medical pretenders.

The meetings of the earlier associations were held at the various members' homes for social converse, literary improvement and the exchange of fraternal courtesies. We later learn that meetings of the Middlesex North District Medical Society were held for thirty years in the Natural History Rooms of the Mechanics Building in Dutton Street, where the Genoa Club is now located. The first meetings held were in the nature of clinics where patients were examined free by three or more selected members. This practice was soon discontinued, and case reports were discussed, often with autopsy findings. Later, scientific papers were presented by members who were selected alphabetically. During the last twenty-five years the papers have usually been given by members of the profession from the large centers and teaching institutions.

It is interesting to note the subjects of some of the addresses given in those early days at the meetings. For instance, Dr. John C. Dalton spoke on "Certainty in Medicine." One wonders just how much closer we have approached to "certainty" since that time. Dr. Zadok Howe, a family physician of Billerica, spoke of "Fear in Connection with Medicine." Without doubt this was the first psychiatric address ever given in this county. Fortunately, perhaps, he did not have the Freudian advantages of the modern-day specialist. "Cholera" was the subject of an address given by Dr. J. O. Green at a time when the disease was prevalent in the county. He also included in his paper a report drawn up by him as a member of a delegation consisting of himself, Dr. Bartlett and Dr. Huntington. These men had been appointed to investigate and report the nature, remedies and preventives of cholera, and were sent to New York by the selectmen of Lowell, one of whom was Dr. Josiah Crosby. This is early evidence of the importance of our society in its constant attention to affairs concerning the general public health.

The reports of the earlier meetings show that they were not so harmonious as those we are accustomed to attend. In fact, if it had not been for our legal connection with the state society, the district association would have been abandoned, since the dissensions among members were often long and loud. The subject of the controversies was usually based on questions of ethics and methods of practice.

There were periods when the meetings were not well attended. In 1879, it was voted that the meetings be followed by a dinner and the attendance was greatly increased with an interest that has never since lessened. The oft-repeated expression, "The way to a man's heart is by his stomach," is the keynote to the revival of this society.

Some of the most heated and lively discussions occurred at times when the community was in the throes of epidemics of scarlet fever, diphtheria, typhoid fever, meningitis, smallpox and cholera. The mere naming of this list of diseases, which were most prevalent in epidemic form during the early period of this society, impresses on one the tremendous advances that have been made in medicine since that time.

In those days, as now, the physicians and surgeons gave generously of their time and skill to charity. Of course they had a fee table, and it may be interesting to note some of the charges.

For a visit within one mile	$.75
Each additional mile	.25
Visit in night (night is understood as beginning at 10 p.m. and ending at sunrise)	1.00
Advice in ordinary office cases	.25
Advice in ordinary office cases and medicine	.50

Small dressings at office	.50
Extracting tooth	.50
Each additional tooth	.25
Obstetrical case	5.00
Amputation of fingers and toes	1.00 each
Reducing fracture of large limbs	5.00

Obviously there was no inflation in those days.

It was stated in an editorial of the *Boston Medical and Surgical Journal* in 1847 that Lowell in 1846 contained 28,841 inhabitants. In that year there were 690 deaths; "pulmonary consumption," as everywhere in New England, swept off the greatest number, and scarlet fever was the next active agent in destroying human life. In the field of surgery, on the other hand, in another two years the world will be celebrating the hundredth anniversary of the greatest boon to modern surgery, namely, ether. It was only two years after the founding of our society that, within twenty-five miles from here, at the Massachusetts General Hospital, occurred the first public demonstration of the anesthetic properties of ether.

With the banishing of pain in operative cases there was still the specter of infection remaining, as in erysipelas, pyemia, septicemia, and gangrene, from which no surgical patient was safe. The work of Pasteur demonstrated that organisms and bacteria, airborne and otherwise, were the source of wound infections, following which Lister attempted to prevent infection by antiseptic methods. It was later in the eighties that the modern aseptic technic was developed. All this time members of our society were at work here in Lowell, first at the Corporation Hospital, where Kimball did his original and pioneer work under antiseptic methods, and later at St. John's Hospital, where aseptic technics were introduced and developed by some of our keen and progressive members.

Our fellows were well aware of the newer discoveries by engineers and scientists in public-health matters. Several members were the instigators and organizers of the Massachusetts Public Health Association.

In the early days of our society, the practice of medicine was more of an art than a science. It was largely carried on in patients' homes or doctors' offices. The doctors early learned that the best work could be done in hospitals, of which we have three — the old Corporation Hospital, organized in 1839 and now known as St. Joseph's Hospital; St. John's Hospital, founded in 1865; and the Lowell General Hospital, founded thirty years later.

The latter part of the century had become an age of science. Such diseases as tuberculosis, diabetes, pernicious anemia and some cases of cancer were no longer necessarily mortal diseases.

Within a few months following the publishing of the original paper describing the discovery of x-rays, forty-nine years ago, an x-ray picture of a coin and hairpin was taken through a book with an apparatus set up at the Lowell High School by Cyrus W. Irish and Dr. J. Arthur Gage. This is an example of the alertness of our members to the importance of new scientific discoveries and their possible clinical application.

In the lifetime of this district society there has been more advance and progress in medical science than in all the centuries that preceded. One wonders what science will offer in the future. I hope, however, that a hundred years from tonight the menu will not consist of a couple of capsules and an intravenous infusion administered by a white-garbed nurse to each as he enters the banquet hall.

As I stated earlier that we like people better than dates let us turn to some interesting and important personalities outstanding in the history of our society.

Among the men who led in conducting the affairs of the society in those early years are the following first officers elected: Dr. Nehemiah Cutter, of Pepperell, president; Dr. Elisha Huntington, of Lowell, vice-president; Dr. John D. Pillsbury, of Lowell, secretary; Dr. J. P. Jewett, of Lowell, treasurer; Dr. J. W. Scribner, of Lowell, librarian; and Drs. Augustus Pierce, of Tyngsboro, Elisha Huntington, of Lowell, and Harlin Pillsbury, of Lowell, members of the Standing Committee.

Dr. David N. Patterson wrote necrologies of the physicians of Lowell and vicinity from the year 1826 to 1898, and to him must be given credit for recording much of interest in connection with our society, including the sketches of the lives of many of the more prominent members.

There have been many distinguished fellows of the Middlesex North District Society, and it would be a great injustice to the memory of those fine and able men if some recognition were not given to their labors at this centennial celebration.

Among the many physicians who have practiced in this city is one who by his original views and fearless conduct was far in advance of his times as a medical practitioner and writer. Dr. Elisha Bartlett was a highly accomplished scholar and physician. He was an extremely popular medical teacher and a ready lecturer. He also attained great eminence as an author, and his published books and pamphlets, both professional and miscellaneous, are numerous. He held various professorships in the Berkshire Medical Institution at Pittsfield, the Medical Department at Dartmouth College, Louisville University and the medical college at Woodstock, Vermont.

It is an honor to the medical profession that one from its ranks was chosen to be the first mayor of this city. It was a mark of special distinction that this responsible trust should have been bestowed on Dr. Bartlett when only thirty-two years of age. Dr. Oliver Wendell Holmes, a lifelong and intimate friend of Dr. Bartlett, when speaking of his death remarked that his loss was a national calamity.

In 1824, two years before the incorporation of the town of Lowell, there came into this place a young

man possessing unusually promising traits of character. These and other excellent qualities were united in the person of Dr. Elisha Huntington. He was an able physician of rare culture and scholarly attainments. As a family physician he enjoyed the confidence and high regard of a large number of families in this community, who retained his services as long as he lived. Charity to the poor was one of his marked characteristics. Dr. Huntington, in presiding at the head of the municipal government, finished a career that has never been excelled in local history. In 1856 he entered for the seventh time on the duties of mayor. So long as the fame of this city shall survive, the public services of Dr. Huntington will live on Lowell's records, and his name will occupy a prominent place in its history.

Prominent among the early physicians stands the name of John C. Dalton. Dr. Dalton was an ardent lover of his profession, and gleaned those acquisitions that enabled him to take high rank not only with his local medical associates but among the leading physicians of the Commonwealth. The entrance of a young physician into professional life in those days was somewhat different from the usual custom of later years. In some respects it was not unlike that of a minister receiving a call to serve a parish. Dr. Dalton virtually received a call from the people of Chelmsford, and it was extended in the following manner. In 1818 Dr. Wyman, who was then practicing at Chelmsford but had received an appointment as superintendent of McLean Asylum, was requested by the citizens of the town to appoint a successor. On his recommendation, Dr. Dalton, then in his twenty-third year, began his practice.

An amusing incident, as related by Dr. Dalton, occurred on his first coming to Chelmsford, the mother town of Lowell. Dr. Wyman took him around to different parts of the town and introduced him to the leading families, speaking a good word in his behalf, for he looked very youthful as compared with Dr. Wyman. In calling on one of the principal families, its head, a man remarkable for age and wisdom, after making a survey of the "young doctor" remarked that a physician would have to fill more than one graveyard before he had a chance to experiment on him. Notwithstanding the shock this remark made on the young Dr. Dalton at the time, this family became one of his best patrons.

Very few men have had the distinction of having four eminent sons as did Dr. Dalton. Two of them became noted physicians, and through the generosity and interest of one of the other sons a substantial sum, long known as the Dalton Scholarship Fund, was established for medical research at the Massachusetts General Hospital.

A bold and daring pioneer surgeon of this city who, through his explorations in uncharted surgical fields, before the discoveries of Louis Pasteur and Lord Lister, contributed much to medical science for the relief of suffering humanity was Dr. Gilman Kimball. When the Lowell Corporation Hospital was established, Dr. Kimball was elected physician-in-charge. He was retained in this position for twenty-six years.

Dr. Kimball was one of the first in the practice of ovariotomy in this country. There is no other operation known to medical science that early met with such decided opposition on every hand as did this branch of operative surgery. The mortality was large. At that time the whole number of surgeons in this country who had ever performed this operation was less than ten. Before Dr. Kimball's death he performed ovariotomy in 300 cases. According to Dr. Howard Kelly, of Johns Hopkins, Dr. Kimball has the distinction of being the first surgeon to perform successfully the removal of the whole of the uterus based on a correctly established diagnosis. He performed this operation in 12 cases, with 6 recoveries. In 1842, he was elected to succeed the brilliant Dr. Willard Parker, of New York City, — one of Chelmsford's gifted sons, — as professor of surgery in the medical college at Woodstock, Vermont, and in the following year he was chosen to fill a similar position in the Berkshire Medical Institution at Pittsfield, Massachusetts. His name will pass into history as one of the foremost surgeons of this country.

At this time, mention should be made of some of the leading surgeons and physicians of the latter part of the century just closed, who can still be remembered by many. One whose name is familiar to all is Dr. Moses Greeley Parker. Through his generosity he made it possible for the people of this district to enjoy the best in music, literature and art, as well as lectures on travel, health and hygiene. As a benefactor to the society he left a fund to provide dinners at the meetings similar to the well known Cotting Lunch Fund of the Massachusetts Medical Society. Others are Dr. John C. Irish, a leading and skillful surgeon, and his two apt and able pupils Dr. Robert E. Bell and Dr. Joe V. Meigs, who were eminently successful surgeons. Dr. Francis C. Plunkett was a beloved family physician and an original staff member at St. John's Hospital, where he served actively and ably for many years. Dr. George H. Pillsbury was a cultured medical gentleman, whose father, Dr. Harlin Pillsbury, was one of the charter members of this society.

One of the society's most energetic members during the last years of the century, who through his clear vision and forcible speaking was able to unify the profession in matters calling for firm and advanced action, was Dr. J. Arthur Gage. In 1930 this society tendered to Dr. Gage on his retirement a farewell banquet in testimony to his great worth and value to the community that he had served so well, for he was an acknowledged leader.

Finally, it may be said that the lives of these men who acquired, both in medicine and in other fields of civic endeavors, honorable distinction

among their contemporaries stand out as steps of progress in the growth of our society. Others equally deserving could be mentioned if time permitted.

The society has always had its quota of physicians in the Medical Corps of the United States Army and Navy. Not only in the Civil War and World War I have the doctors of Middlesex North District Medical Society taken an active part, but in the midst of World War II this society is well represented on all war fronts. We are proud of their work and the spirit that carries them on. If it were possible, they would be here with us tonight. Since this cannot be, our earnest wish is that our prayers will be answered and that these young men may come back to us safely. On their return after this conflict may they find that our association is appreciative in full measure of their unselfish efforts and the unfailing sacrifices that they have made. Furthermore, not only does the society know their true worth, but the wounded and sick soldiers know its members' skill. They also have felt the warmth of heart and sincerity of our profession.

When, in the course of time, another century of this society's existence shall have passed into history, the men then taking our places, even with their advances in the knowledge of medical science, can surely take an honest pride in the efforts, experiences and accomplishments of the physicians of the century just closed.

EARLY RISING AFTER SURGICAL OPERATIONS

JOSEPH ASHKINS, M.D.*

MILFORD, MASSACHUSETTS

THE question of when a patient should arise following an operation is one concerning which there has for many years been considerable divergence of opinion. There has been an increasing tendency to get patients out of bed early, but few surgeons, particularly those of this country, have advocated that patients walk from the operating table or become ambulatory twenty-four to forty-eight hours postoperatively. Surgeons who have adopted this routine claim that all postoperative complications such as pneumonia, wound infection, thrombosis and embolism are less frequent than they are in the mobilized patient. Shortly after the turn of the century, largely owing to the work of Ries,[1] of Chicago, and Kümmell,[2] of Hamburg, early postoperative rising had many advocates, but this routine gradually fell into disrepute until recently.

In 1937, Kimbarovskiy[3] reported on 551 cases. Of 71 patients operated on for hernia of the linea alba, all walked from the operating table and 96 per cent were discharged not later than the seventh day after operation. Of 124 patients with inguinal or femoral hernias, 67 per cent walked from the operating table and 29 per cent arose on the following day; 94 per cent were discharged not later than the eighth day after operation. Of 210 patients with chronic appendicitis, 84 per cent arose on the following day; 79 per cent were discharged not later than the seventh day after operation. Finally, of 146 patients who had a gastric resection for ulcer, 63 per cent arose on the second hospital day and 26 per cent on the third; 42 per cent were discharged not later than the ninth day after operation. Kimbarovskiy is convinced that the incidence of postoperative pneumonia, wound infection, thrombosis and embolism is lowered and that the incidence of hematoma and wound disruption is not increased in such patients.

In a subsequent paper he[4] states that in a series of 1600 patients handled in this manner, the incidence of thrombosis and embolism was only 0.2 per cent. In the same paper he reports concerning experiments with 30 dogs. In all, the abdomen was incised in the midline and the stomach was incised. Half were kept recumbent and half were allowed complete movement, equal numbers of each group being killed on the fifth, seventh and ninth days. The scars in the stomach and abdominal wall were examined microscopically; those of the stomach were identical in both groups, whereas those of the abdominal wall showed much better healing in the active group than in the immobilized group.

In 1940, Niedeggen[5] published an account of 1646 patients who were induced to leave their beds within twenty-four hours of operation if they had been ambulatory before it was performed and if they did not have a high fever. On the morning after operation, a nurse raised the upper part of the body from the pillow and another swung the legs over the edge of the bed. The patient was assisted to his feet and walked about the room for several minutes, being supported on both sides, and then was helped back to bed. This was repeated six hours later. On the second day, most of the patients were attended with little difficulty and many of them had their meals at a table. By the third or fourth day, little was required in the way of special care, and on the fifth or sixth day, it was not unusual to see patients walking in the garden or making themselves useful about the hospital. If there was marked exaggeration of

*Surgeon, Milford Hospital.

wound pain, it was almost always due to an incorrect technic in getting up or to dressings so applied that pressure or traction resulted. In the entire series the incidence of thrombosis and phlebitis was 0.5 per cent, and 0.35 per cent of these patients had evidence of embolism. The operative mortality was 0.18 per cent, and not a single case was lost because of a pulmonary infarction. The types of operation are not given, but it is stated that of 51 patients who underwent gastric operations only 1 had a postoperative bronchitis and none had a subsequent pneumonia.

In 1938, Campeanu[6] reported the end results in 1300 cases in which the patients either walked away from the operating table, if local anesthesia had been used, or arose from their beds as soon as paralysis had disappeared, if spinal anesthesia had been employed. The most frequent operations were as follows: appendectomy, 682 cases; phrenectomy, 165 cases; herniotomy, 126 cases; gastroenterostomy, 42 cases; gastric resection, 33 cases; resection of adhesions, 32 cases; and cholecystectomy, 28 cases. The operative mortality was 0.23 per cent, and not a single patient had a complication that could be attributed to early rising. Certain patients who had had an appendectomy or herniotomy left the hospital on the day of operation, and the majority had left by the third or fourth day, returning on the seventh day to have the stitches removed.

In this country, Leithauser and Bergo,[7] in 1941, reported 436 cases in which the patients got out of bed soon after operation and were permitted to be ambulatory. The majority (370) of these patients suffered from acute or chronic appendicitis without evidence of spreading or generalized peritonitis. In the remaining patients the three most frequent operations were cholecystectomy (18 cases), herniorrhaphy (9 cases), hysterectomy (7 cases) and other pelvic procedures (6 cases). In the cases of appendectomy, the average number of days of confinement was 1.5 days and the average hospital stay 2.3 days. For the other cases, the figures were 1.9 days and 8.9 days, respectively, and the patients who were active on the first day had the most favorable convalescences. There was a single fatality due to a massive hemorrhage from jejunal ulcers, on the seventh postoperative day. Otherwise, there were no complications such as wound dehiscence, hernia, pneumonia and thrombophlebitis. These authors believe that early rising and graduated ambulatory activity increase the rate and depth of breathing and the tone and use of skeletal muscles, thus improving the circulation in the pulmonary, systemic, portal and lymphatic systems, and that they probably promote the return of normal function of the vital organs and aid elimination through the kidneys.

Charbonnier[8] starts his patients with deep breathing exercises and movements of arms and legs in bed during the period before rising, beginning as soon as the patient has come out from the narcosis. His patients are never allowed to rise before the third postoperative day and are usually allowed to do so on the fourth postoperative day. In some cases they are kept in bed until the fifth day. In a series of 408 patients who underwent laparotomy there were only 17 who had postoperative complications; practically all these complications were minor, and none could be attributed to early rising. There was no case of eventration or of pulmonary embolism, and there were no deaths.

Harild[9] is opposed to early rising after laparotomy, chiefly because of reduction of the minute volume of the blood in connection with operation. In support of his position, he has made a study of the minute volume in patients who have undergone laparotomy for one of several conditions and in those on whom extra-abdominal operations have been performed. The types of laparotomy represented are appendectomy, laparotomy with ventrosuspension of the uterus, colostomy, exploratory choledochotomy and ventral herniotomy. Two extra-abdominal operations represented are radical extirpation of the breast and arthrotomy of the knee for a lesion of the meniscus. The minute volume was reduced after operation by 30 to 35 per cent, even in cases in which there were no clinical signs of circulatory disturbance. In cases with primary shock, the decrease was even more marked. In most of his cases there was little or no change in the minute volume on the first day after operation, the most marked changes occurring two or three days after it. He also notes that no clinical signs of cardiac deficiency were determinable, indicating that the cause of the changes in minute volume must be in the periphery. On the basis of these findings, Harild concludes that even though operation induces an increase of oxygen consumption there is a reduced minute volume, and that the increased need of the tissues for oxygen must be satisfied by way of an increased discharge of oxygen from the blood. On the basis of these findings he believes that it does not seem justifiable to permit patients to leave their beds after laparotomy, at a time when there is partial circulatory insufficiency.

Lindhart[10] and other investigators have found that the transition from the supine to the sitting or standing position induces a reduction of the cardiac minute volume, and the experiments of Asmussen, Hohwu, Christensen and Nielsen[11] published in 1939, show that the circulation in the passive standing position must be looked on as actually insufficient. In this position, a considerable amount of blood, up to 500 cc., accumulates in the lower extremities. They believe that patients should lie abed until the circulatory deficiency has run its course, which requires from five to ten days and sometimes longer, depending on the gravity of the operation and possibly the type of anesthesia. Since a similar study was not conducted on those who arose early,

these findings can only be properly interpreted as showing what happens in the quiescent postoperative patient.

Leithauser,[12] in studying the vital capacity of 202 patients subjected to early rising, made readings each day in the lying, sitting and standing positions before and after surgical procedures on the abdomen. After early rising, the vital capacity returned to normal in half the prescribed period; convalescence closely followed the improvement in vital capacity. He believes that coughing exercises in the standing position are specific therapy for the rales and possible mucous plugs that may be present following operation.

In a review of the literature, Newburger[13] notes the unfortunate experiences with early postoperative activity when coarse suture material and running stitches were used in closing the abdomen, many case histories ended with the notation, "On the tenth day they returned to the hospital with their guts in a napkin."

* * *

The patients who occasionally became ambulatory, and even violent, immediately after operative procedures as a result of accident or intercurrent disease and suffered no ill effects stimulated my interest in the possible advantages of early rising.

It was decided to allow young patients who were in good physical condition and who had undergone simple appendectomy to leave their beds as soon as they felt able. This usually occurred on the third or fourth day after operation. After a few months' experience, this same type of patient was urged to arise even earlier. Most were apprehensive and had to be assisted and encouraged, and it was with real trepidation that they took their first steps. These patients were not premedicated before becoming ambulatory, nor were they given lengthy encouragement. The nurses merely entered the room and requested the patient to rise and offered their assistance. Those who objected, a small percentage, were not forced to rise, but were encouraged again the next day and told that it was better for them to be out of bed early. Once up, they seemed particularly pleased in their ability to get along, and it was not difficult to keep them ambulatory. They were allowed to stay up for half an hour in the morning and half an hour in the afternoon. The period was lengthened each day, until on the fourth day the patient was in bed for only a short period in the morning and another in the afternoon. Emphasis was placed on the importance of walking. The patients were not merely moved from their beds and allowed to sit in chairs.

During the first day, the patient was usually rigid and apprehensive about moving and did not enjoy the procedure. On the second day, however, there was evidence of increased ability to move around. By the fourth day the patients walked with comparative ease and could be found reading, lounging about or taking short walks without hesitation. Occasionally they reached this stage on the third postoperative day.

This method of treatment was gradually extended to include most postoperative patients except those too ill as a result of severe infection, previous disability or unusually severe postoperative reactions.

In patients subjected to more extensive procedures, such as cholecystectomy and hysterectomy, the routine was modified and they were allowed out of bed for ten minutes on the morning of the first postoperative day and again in the afternoon. They were occasionally given an opiate before rising. It was not until the third or fourth day that they stayed up for an hour at a time. Of the latter group, 20 per cent were unwilling to leave their beds until the second or third day.

The operative wounds in these cases were closed in a variety of ways. In all of them tissues were accurately approximated and bleeding points ligated. For a few years, silk was used to repair the fascia. At present, silk and fascia are being utilized in the repair of hernias, and other abdominal incisions are routinely closed with continuous No. 0 chromic catgut to the peritoneum, interrupted No. 1 chromic catgut to the fascia, No. 000 chromic catgut to the subcutaneous tissue and black silk to the skin. The suture material used for vaginal plastics is No. 0 or 1 chomic catgut. In upper abdominal longitudinal incisions, after suturing the peritoneum in the usual fashion, the rectus muscle is retracted. Almost invariably the transversalis fascia is found to be gaping in the superior half of the incision. It is impossible in most cases to close the peritoneum and transversalis fascia accurately with a single row of sutures, and many postoperative hernias may arise from failure to recognize this fact. In one follow-up of 393 patients operated on for gall-bladder disease, 12.9 per cent developed incisional hernias.[14]

In the present series of 823 patients who were out of bed on the first to third postoperative day (Table 1), there were no serious complications due to their early mobility.

These patients are instructed to return to the office for their first checkup in four to six weeks after operation. At the end of three months, another examination is made. If they are normal at that time, they are dismissed but are told to return if anything unusual occurs. Since many of these patients are from surrounding towns, the referring physicians usually make the succeeding examinations.

The following four complications have occurred. One patient, on whom a cholecystectomy was done, appeared normal at the first examination but later his physician stated that the operative wound was bulging and instructed him to wear a belt. Another patient, operated on for a recurrent inguinal hernia,

developed a thin area in the upper third of the operative wound six months after leaving the hospital. Protrusion does not exist at present, but it seems likely he will have a recurrence. A pulmonary infarct into the lower left lobe occurred in an obese male on the seventh day after he had been operated on for a gangrenous appendix. Recovery was complete. The fourth patient, admitted with a ruptured appendix, ran an uneventful course until the eighth postoperative day, when she began to complain of pain in the calf of the right leg. Local tenderness, swelling and a positive Homans's sign were present. The thrombophlebitis remained localized, although slight swelling of the ankle persisted six months later.

All these patients were out of bed within twenty-four hours.

TABLE 1. *Types of Operation in Patients Submitted to Early Rising.*

TYPE OF OPERATION	YEAR								TOTAL NO. OF CASES
	1937	1938	1939	1940	1941	1942	1943	1944	
Appendectomy	56	50	57	33	58	82	71	74	481
Herniorrhaphy:									
Incisional	—	—	—	—	—	3	1	2	6
Inguinal	—	—	—	12	14	18	24	38	106
Femoral	—	—	—	—	4	1	3	2	10
Cholecystectomy	—	—	—	—	12	10	13	22	57
Abdominal operations for uterine displacement or disease of its appendages or both	—	—	—	4	5	10	18	28	65
Abdominal hysterectomy	—	—	—	—	5	3	16	14	38
Vaginal hysterectomy	—	—	—	—	—	—	7	3	10
Anterior and posterior colporrhaphy	—	—	—	—	—	4	10	12	26
Lysis of adhesions for intestinal obstruction	—	—	—	—	—	1	3	2	6
Suprapubic prostatectomy	—	—	—	—	—	—	1	2	3
Suturing of perforated duodenal ulcer	—	—	—	—	—	—	—	2	2
Cesarean section	—	—	—	—	—	—	5	6	11
Nephrectomy	—	—	—	—	—	—	1	1	2

CASE REPORTS

CASE 1. J. C. (47706), a 72-year-old man, was admitted to the Milford Hospital on January 21, 1944, with a history of acute upper abdominal pain starting 36 hours previously. He was seen by his physician, who gave him 16 mg. of morphine, which brought partial relief. The following morning he was having chills and vomited repeatedly. He was again given morphine and experienced some relief. During the day he became progressively worse and was admitted to the hospital that evening.

On examination he appeared ill and uncomfortable. The temperature was 100.2°F., the pulse 94, the respirations 28, the blood pressure 140/76, and the white-cell count 21,400. The heart sounds were of good quality, with an occasional extrasystole. The chest was hyper-resonant, with many dry rales throughout both lungs. There were spasm and rigidity in the right upper quadrant of the abdomen, with maximum tenderness at a point 4 cm. lateral and somewhat superior to the umbilicus.

The diagnosis of an acutely inflamed gall bladder was made. The patient was given 5 per cent glucose in normal saline solution intravenously. After receiving 1500 cc., he was taken to the operating room with the drip still running at a rate of 60 drops a minute. Under nitrous oxide, oxygen and ether, a right upper rectus muscle-splitting incision was made. When the abdomen was opened, a swollen, tense, thick-walled gall bladder adherent to surrounding structures was found. It was freed by sharp and blunt dissection and walled off. An incision was made 1 cm. from the liver edge on the anterior surface of the gall bladder. It was deepened until a line of cleavage was made out, and the dissection was carried downward on the medial and lateral surfaces until the gastrohepatic omentum was reached. This was carefully dissected, exposing the cystic duct and artery. They were doubly ligated and the gall bladder was removed. There was moderate oozing from the gall-bladder bed; it subsided promptly. Five grams of sulfanilamide powder was scattered widely throughout the operative area and a drain was inserted to the foramen of Winslow. The peritoneum was closed by continuous No. 0 chromic catgut, as was the transversalis in the upper portion of the wound. Three silk stay sutures were inserted, the fascia was closed by interrupted No. 1 chromic catgut, and black silk was used for the skin. The operation began at 12:45 a.m. and was completed at 1.20 a.m. The patient left the table in good condition.

When seen the following morning the patient appeared cyanotic. The respirations were audible outside the room. There were many moist rales throughout both lungs. A diagnosis of so-called "massive collapse" was made. The patient was placed on his feet, instructed to cough, walked a few steps and returned to bed. The cyanosis disappeared and the patient breathed comfortably, with but a few moist rales remaining. From then on, the postoperative course was uneventful. He was out of bed and walking each morning and afternoon. On the 4th postoperative day his general condition was good and he was eating well. He was discharged on the 6th day. At the last postoperative checkup, made on June 15, the operative wound was firm and nontender and gave no evidence of hernia.

CASE 2. H. W. (46869) a 47-year-old, obese woman, was admitted on September 14, 1944, with a history of having been under treatment for the last 2 years for menopausal symptoms. Five weeks previously, she began to bleed vaginally. One week before admission her physician examined her, stated that she had a fibroid uterus, and advised operation.

The general physical examination was essentially negative. On bimanual examination, the fundus was palpable 2 fingerbreadths above the symphysis. It was smoothly irregular, slightly tender and movable and filled both vaults. The cervix was hard and smooth but not otherwise remarkable.

On September 16, under nitrous oxide, oxygen and ether, a supravaginal hysterectomy was done after the manner of Curtis.[15] During the first 24 hours the patient received 1000 cc., of 5 per cent glucose in normal saline solution and 2000 cc. of 5 per cent glucose in distilled water. She appeared comfortable on the morning after the operation. She was given 16 mg. of morphine and half an hour later, with one nurse lifting her feet and another supporting her shoulders, she was placed in a sitting position on the side of the bed. After a short interval, she was helped to step to the floor and was assisted in walking about the room. She sat in a chair for 10 minutes, walked back and was helped into bed. This process was repeated twice a day. On the 2nd and 3rd postoperative days she had a few gas pains with no visible distention. By the 5th day, with a nurse lending slight support, she was walking with assurance and appeared quite comfortable. She was discharged on September 25 with the wound healing by first intention and with no evidence of infection.

Her physician did the postoperative checkups and reported that she had had an uneventful convalescence.

CASE 3. M. N. (47867), a 26-year-old woman, was admitted on February 17, 1944, at term and in active labor. The head was not engaged. She was given a test of labor lasting

for 14 hours, but the head still failed to engage. She was then moved to the operating room for cesarean section.

Under nitrous oxide, oxygen and ether, a low midline incision was made. The peritoneal reflexion of the bladder was turned downward, and retractors were put in place. A transverse incision was made through the lower uterine segment. Unusually severe bleeding occurred from the uterine walls and was controlled by clamps. A living male child was extracted and 0.2 cc. of Pituitrin was given intravenously. When the uterus began to contract, the placenta was removed. The incision in the uterus was closed by an inner layer of No. 1 chromic catgut sutures and an outer layer of interrupted sutures. Peritoneal reflexion was restored to cover the suture line. The pelvis was wiped out and the abdomen closed in layers, using No. 0 chromic catgut for the peritoneum, No. 000 chromic catgut for the subcutaneous tissue, No. 1 chromic catgut for the fascia and black silk for the skin. The patient left the table in good condition. Postoperatively she was given 1500 cc. of 5 per cent glucose in normal saline solution, 11 mg. of morphine as needed to relieve pain and 1 cc. of ergotrate every 4 hours intramuscularly until she was able to retain tablets by mouth.

The following morning she appeared in good condition and was assisted out of bed, walked a few steps and sat in a chair for 10 minutes. This process was repeated each morning and afternoon, the ambulatory periods becoming longer as her strength returned. The temperature for the first 3 days did not go above 100°F., and from then on it remained normal. She was instructed to be active while in bed and had only slight abdominal distress for the first 3 days. The sutures were removed on the 8th day. The wound was clean and firm, and as the patient's general condition was good she was able to get in and out of bed with slight assistance and had no difficulty in walking. Her appetite was good, and she was allowed to go home.

A postnatal checkup 8 weeks later revealed no evidence of prolapse. The abdominal incision was firm, and there were no abnormalities.

Case 4. H. B. (43642), a 56-year-old man, was admitted on May 31, 1942, with two large, painful inguinal hernias and a history of asthma and chronic bronchitis. He experienced respiratory distress if kept in a recumbent position for any length of time because he could not clear the mucus that accumulated in the bronchial tree.

On June 1, under nitrous oxide, oxygen and ether, a bilateral repair was done. After dissection of the hernial sac and return of its contents into the abdominal cavity, the sac was ligated at its base by interrupted sutures. A portion of the conjoined tendon, fascia and muscle of the internal oblique was attached to the inguinal ligament by interrupted silk sutures and by a strip of fascia taken from the external oblique, whose medial attachment to the symphysis was not disturbed. It was impossible to secure fascia-to-fascia approximation without placing sutures under tension, so that, in the upper third of the repair the muscle of the internal oblique was attached to the inguinal ligament. The defect in the external oblique was repaired by silk, the subcutaneous tissue was approximated by No. 000 chromic catgut, and black silk was used for the skin.

The patient was out of bed the following morning, walked about the room and spent considerable time in a chair. He required 1 cc. of 1:2000 Prostigmin on the 2nd and 3rd days for relief of abdominal distention. His chronic cough was only partially controlled by codeine. He was unusually active during the 11 postoperative days spent in the hospital.

His physician reported that there was no evidence of recurrence when he was last seen 1 year after the operation.

Case 5. C. C. (46361), a 71-year-old, well developed but poorly nourished woman, was admitted on July 13, 1943, with a history of vaginal prolapse of 4 years' duration, causing increasing discomfort and disability. She consulted her physician, who advised surgery.

The general physical examination was essentially negative, and the findings were consistent with the patient's age. There was complete prolapse of the uterus without ulceration of vaginal mucous membrane or cervix.

On July 15, under nitrous oxide, oxygen and ether, vaginal hysterectomy was done, following the technic of Adams.[16]

The 2nd day after the operation she was helped out of bed and walked a few steps. She was up each morning and afternoon for 10 minutes. By the 7th day she was walking with slight assistance and remained in a chair for an hour at a time, although she complained of occasional discomfort in the perineum. There was a rather profuse vaginal discharge, which cleared up slowly, and she chose to remain in the hospital until it was practically gone. She was discharged on August 7.

Her physician reported that her condition has remained excellent, with no evidence of prolapse.

Summary

The dangers of prolonged postoperative bed rest, particularly in the obese and aged, are becoming more generally recognized, and there appears to be a favorable clinical response to early rising.

On the basis of a review of published cases and personal experiences, it seems safe to allow patients out of bed within twenty-four hours after operation in the majority of cases.

36 Pine Street

References

1. Ries, E. Some radical changes in aftertreatment of surgical celiotomy patients. *J. A. M. A.* **33**:454-456, 1899.
2. Kümmell. Cited by Newburger.[13]
3. Kimbarovskiy, M. A. Rannee vstavanie v posleoperatsionnom periode. *Nory khir. arkhiv* **35**:57-74, 1935.
4. *Idem.* Rannee vstavanie i zachivlenie posleoperatsionnikh ran. *Nory khir. arkhiv* **48**:116-121, 1940.
5. Niedergen, G. Erfahrungen und Erfolge des Frühaufstehens nach Operationen. *Zentralbl. f. Chir.* **67**:954-958, 1940.
6. Campeanu, L. 1300 operati si alzano direttamente dal tavolo operatorio. Il movimento promotore della guarigione. *Arch. ital. di chir.* **51**:12-23, 1938.
7. Leithauser, D. J., and Bergo, H. L. Early rising and ambulatory activity after operation: means of preventing complications. *Arch. Surg.* **42**:1086-1093, 1941.
8. Charbonnier, A. Le traitement post-opératoire des laparotomisés par la "méthode du lever précoce." *Helvet. med. acta* **9**:166-182, 1942.
9. Harild, S. Soll man nach Laparotomien früh aufstehen lassen oder nicht? *Chirurg* **12**:703-707, 1940.
10. Lindhart. Cited by Harild.[9]
11. Asmussen, Hohwu, Christensen and Nielsen. Cited by Harild.[9]
12. Leithauser, D. J. Confinement to bed for only twenty-four hours after operation. *Arch. Surg.* **47**:203-215, 1943.
13. Newburger, B. Early postoperative walking. II. Collective review. *Surgery* **14**:142-154, 1943.
14. *The Cyclopedia of Medicine Service.* 1053 pp. Philadelphia: F. A. Davis, 1944.
15. Curtis, A. H. *Obstetrics and Gynecology.* Vol. II. Philadelphia: W. B. Saunders Company, 1933.
16. Adams, H. D. Technic of vaginal hysterectomy. *S. Clin. North America* **19**:803-810, 1939.

MEDICAL PROGRESS

THE PRESENT STATUS OF ANTIMALARIAL DRUGS

L. Everard Napier, C.I.E., F.R.C.P.*

BOSTON

IN RECENT years much has been learned concerning the use of antimalarial drugs. The significant changes that have occurred will be discussed in the following paragraphs.

Atabrine

Pre-Pearl Harbor Status

At the beginning of 1942, there were a large group of clinicians who had had ten years' practical experience with atabrine (quinacrine, *U.S.P.*: mepacrin *B.P.*). Many of these were enthusiastic about the drug, not only because it provided an alternative drug for the treatment of malaria, but because they believed that it had definite advantages over quinine in the therapy, and certainly in the so-called "suppression," of malaria. If these clinicians hesitated to advocate its adoption in complete supersession of quinine, it was because quinine had a brilliant record of three hundred years' service in the treatment of malaria, because the advantages of atabrine over quinine were quantitative rather than qualitative and because it was thought possible, even if not probable, that chemists would soon synthesize some drug that would surpass atabrine in its antimalarial action. There was another reason, a political and economic one: atabrine was for many years manufactured only in Germany, whereas in several malarious countries — for example, India — quinine and the other cinchona alkaloids were already local products, and in others cinchona cultivation was recognized as possible and was being planned. Other physicians, although admitting the efficacy of atabrine, did not share the enthusiasm of their colleagues and did not believe that its introduction constituted a real advance. Still others actively opposed its use and appeared to take a delight in reporting untoward incidents that occasionally occurred during a course of atabrine therapy, often without distinguishing between its by-effects and the complications of the attack of malaria. Among this last group were the diehards who had an almost religious regard for quinine and considered it sacrilege to question its supremacy. These persons — unwittingly, of course — did a great disservice to progress, since much time had to be wasted in overcoming the strong opposition to the wider adoption of this drug, which they had aroused, among both the medical profession and the laity, by ill-advised public pronouncements.

Early Dosage Regimes

The dosage adopted in the initial clinical trials with naturally acquired malaria was necessarily arbitrary (Peter,[1] Napier and Das Gupta,[2]† Napier, Butcher and Das Gupta[3] and Green[4]). The majority of the patients in these and the later trials during the early years were Asiatics of small stature, and most of them were partially immune, so that, although the standard dosage adopted as a result of wider clinical experience was slightly larger than that used in the initial trials, it was of the order of a minimal dosage. This dosage was 0.1 gm. thrice daily for five days, occasionally extended to seven days, for therapy, and 0.2 gm. twice weekly for suppression.

Despite the satisfactory results of this therapeutic regime, it was noted that the action of atabrine on the parasitemia and fever was slightly less rapid than that of quinine, and for this reason quinine was sometimes recommended for the first two days of treatment, followed by the usual course of atabrine — for example, in the British Army routine (see below).

Pharmacologic Investigation

The pharmacologist was hampered in the early days by the inadequacy of the methods of determining atabrine in the urine, blood and tissues; he did show, however, that it appeared in the urine within a few minutes, whether the drug was given by mouth or intramuscularly, that traces could be detected there for some time, and that it accumulated in the tissues, but he did not provide any data to encourage the physician to modify his empirically adopted dosage routine.

When in 1942 Japan took Java, whence had hitherto come ten elevenths of the world's supply of quinine, the spotlight of medical research was naturally focused on atabrine, the only known synthetic substitute for quinine. After a little valuable time had been lost, on both sides of the Atlantic, by the not unnatural official hesitancy, in view of the doubts expressed by others, to accept atabrine at the value placed on it by the enthusiasts, the plans for its large-scale production were put into operation. At the same time intensive work on the pharmacology of atabrine was undertaken and important results were obtained at an early date. In a world now extremely plasma-level conscious

*Visiting lecturer, Department of Comparative Pathology and Tropical Medicine, Harvard Medical School and Harvard School of Public Health.

†These workers gave 0.6 to 1.2 gm. in four days.

as a result of several years' experience with the sulfonamide drugs, it is not surprising that one of the earliest investigations was aimed at measuring the plasma level achieved by different dosage regimes and the minimum plasma level that is necessary to control the malarial attack. This work was aided by the fact that the methods of accurately estimating atabrine in the body fluids and tissues were much facilitated by the comparatively recently introduced photoelectric and other fluorometers.

These studies, including that of Shannon et al.,[5] led to some important observations, which can be summarized as follows:

The chemotherapeutic activity of atabrine is a simple function of the plasma concentration.

A large percentage — of the order of 90 — of the atabrine taken by mouth or given intramuscularly is fixed in the tissues, and about 3 per cent is excreted in the urine and 6 per cent in the feces in the first twenty-four hours. After administration is discontinued, the rate of excretion falls off rapidly, but traces are found in the urine for many weeks.

On the ordinary daily dosage of the earlier therapeutic regimes, the maximum plasma level is not attained for several days, but once a balance between the intake on the one hand and the rate of excretion and degradation on the other has been achieved, a fairly uniform level in the plasma may be expected. In a large group of persons taking atabrine daily, the mean plasma level is proportionate to the daily dose, but among subjects on the same dose the levels vary considerably; between extremes this variation may be fourfold — for example, from 30 to 120 gammas per liter after 0.3 gm. atabrine daily. In persons taking a regular daily dose, the general rule is that 40 per cent of the final level is reached at the end of the first day and 40 per cent of the deficit is made up each day subsequently, so that 90 per cent of the peak level is attained by the end of the fourth day. If, however, the dosage on the first day is doubled, this plasma level is attained at the end of the second day, and if it is trebled, this near peak is attained on the first day, and the peak level (for that particular dosage) can be maintained subsequently by the ordinary daily dosage. Conversely, when the drug is discontinued, the falling off in plasma level is at the rate of about 20 per cent daily for several days, but traces of atabrine are still present even after eight weeks.

In the suppressive regime of 0.4 gm. weekly, it has been found that the peak level of between 8 and 15 gammas is obtained about the end of the fourth or fifth week, however the dosage is divided, but that by increasing this to 0.6 gm., given in six doses, a level of the order of 15 to 30 gammas, with a mean above 20, is reached within the same period.

The behavior of atabrine is thus in sharp contrast to that of quinine (see below), which appears very early in the blood in relatively much higher concentrations, reaches its peak concentration in about four hours, and falls far below the therapeutic level by the end of twenty-four hours.

The plasma concentration of atabrine necessary to effect a clinical cure in malaria varies both with the host and with the strain of parasite, but it is generally concluded that a minimum level of 30 gammas is required. For suppression, a breakthrough* does not usually occur when the plasma level is above 12 gammas.

Clinical Experience

Field experience with totally nonimmune members of the British, Australian and American fighting forces, who were on the average considerably heavier and better nourished than the often partially immune Asiatics who had formed the bulk of the clinical material on which the earlier dosage regimes had been calculated, soon showed that these dosage regimes were inadequate from the point of view of both treatment and suppression. It also confirmed the opinion held by many of the earlier workers that the importance of the by-effects of atabrine therapy should not be overemphasized, and indicated that these by-effects are less likely to occur in better nourished persons, that some of them can be obviated by such simple measures as taking sodium bicarbonate or glucose at the same time, that most of them — for example, the gastrointestinal disturbances and the mild psychoses that sometimes follow the early doses — frequently do not occur later during the course when some tolerance for the drug has been established (Green[6]) and that they are therefore not an indication for discontinuing the drug altogether, nor even, except in rare cases, for modifying the dosage.

Dosage Revision

The advisability of increasing the dosage of atabrine thus became obvious, and the data that had meanwhile been accumulated made it possible to introduce a rational regime in place of the earlier empirical one. The most important modification that the pharmacologic investigations had indicated was the principle of "loading" the dosage during the early hours of treatment. This applies whether the drug is given by mouth or parenterally. The dosage recommended by the United States Army exemplified this principle. It prescribed the giving of 0.2 gm. of atabrine immediately and every six hours night and day during the first twenty-four hours, a total of 1.0 gm., and reverting to the three-times-daily dose of 0.1 gm. for another six days, that is, 2.8 gm. in all.

*A term indicating the development of clinical malaria during an established suppressive course.

For parenteral medication it is better to use the intramuscular route, since it has no disadvantages as compared with the intravenous one and is probably safer; by the latter route extremely slow administration is essential. In cases in which parenteral therapy is indicated, — for example, in the unconscious patient, — two injections of 0.2 gm. of atabrine in 5 cc. of distilled water are given into the buttocks, one on each side. Administration by the oral routine should be begun as early as possible, but, if for any reason this is delayed beyond six to eight hours, another intramuscular injection should be given and repeated every eight hours until oral therapy can be instituted. To ensure the necessary "loading," the oral dosage prescribed must be such that the total atabrine given in the first twenty-four hours amounts to 1.0 gm., and the usual 0.1 gm., thrice daily, is continued. (For smaller and less well nourished persons some modification of the dosage is necessary, but the loading principle should still be followed.)

This atabrine course does not by any means preclude relapses in natural infections of any of the three commonly encountered malarial species, but it is more effective in this capacity than is quinine or the other cinchona alkaloids, and it results in a longer initial period of freedom from relapses and wider spacing of subsequent relapses in benign tertian malaria; this is to some extent due to the slow rate of excretion of atabrine and its presence in the blood in appreciable quantities for several weeks. In malignant tertian malaria a second course of atabrine after an interval of ten days often results in a radical cure of this infection.

For suppressive therapy a daily dose of 0.1 gm. is given if this regime can be started not less than two weeks before the subject enters a malarious area, but if an earlier entry is likely, the loading principle should be achieved either by doubling the daily dose for the first week and continuing on the usual daily dose of 0.1 gm. or by giving a single loading dose of 0.6 gm. before commencing the ordinary regime (Medical Research Council recommendation).

So-Called "Practical Prophylaxis" in Malignant Tertian Malaria

There is no drug that acts as a true prophylactic in malaria and destroys or prevents the further development of the sporozoites injected by the mosquito. The failure of quinine to do this has been recognized for many years, and it has been repeatedly shown that nonimmune persons subjected to *Plasmodium vivax* infection during a suppressive course of atabrine, although they remain free from clinical symptoms while on the suppressive treatment, invariably come down with a clinical attack of malaria between the second and fourth weeks after they discontinue the suppressive regime. It has, however, been shown that practical prophylaxis, at least against the South Pacific strains of *P. falciparum*, can be achieved, — that is to say, by giving 0.1 gm. of atabrine daily for two weeks before and twenty-three days after subjection to a heavy infection by this parasite, the subject is protected from any clinical manifestation of malaria, — and that after the drug is discontinued this freedom from clinical malaria lasts indefinitely unless the subject is reinfected. That this is only practical prophylaxis and not true prophylaxis entailing destruction of sporozoites is shown by the fact that early development of the schizogony cycle does actually take place, — as proved by blood-inoculation experiments, — but it does not reach the clinical threshold.

To summarize, it has been shown that in the administration of atabrine for both the suppression and the cure of malaria, by the adoption of more rational regimes, indicated by recent investigations, most of the disadvantages hitherto associated with its use can be overcome, and that in both capacities, and unquestionably in the former, it is the drug of choice. Given in suppressive doses it is apparently a practical prophylactic in *P. falciparum* infections of the South Pacific.

Plasmochin

Plasmochin (pamaquine, *U.S.P.*: pamaquin, *B.P.*) was introduced by Schulemann, Roehl and their co-workers (Roehl[7]) at Leverkusen in 1924 as a synthetic substitute for quinine, after preliminary screening experiments with *P. relictum* infections in canaries. It did not live up to the early claims made for it by its introducers, but it did find a place in the therapeutics of malaria. It was soon shown that by itself it was not a practical drug for use in the treatment of the malarial attack. It stopped the schizogony cycle and cured the clinical attack in both benign tertian and quartan malaria, but only when given in large and toxic doses, and even in these doses it did not affect the clinical attack or the schizogony cycle in malignant tertian malaria. On the credit side, however, it was found to destroy, or at least sterilize, the circulating gametocytes, particularly in malignant tertian infection, in small and perfectly safe doses — 0.01 gm. twice daily for three days. Although gametocyte destruction is not a measure that in any way aids the patient, it is in certain circumstances an important precaution as a prophylactic measure for the general population in a malarious country, and in this capacity plasmochin occupies a unique position, even today, because neither atabrine nor quinine achieves this. Further, it was found that although little was gained by adding plasmochin to quinine so far as the current attack of malaria was concerned, it was of value in reducing the number

of relapses in benign tertian malaria,* but here again only when given in doses that were toxic to the majority of the subjects, and so toxic to a few that the treatment had to be abandoned.

When atabrine was introduced, the assumption that this drug could be used instead of quinine in the quinine-plasmochin antirelapse regime was somewhat too readily assumed. It was believed that the toxicity of each drug was enhanced by its association with the other, so that the dosage of plasmochin was whittled down and it was given separately instead of coincidentally with atabrine. Claims for the relapse-preventing properties of the plasmochin-atabrine combination† were not of the same order as those made for large doses of plasmochin and quinine, but undoubtedly some of the aura that had been generated by the latter gathered around the former combination, and an exaggerated idea of the value of the addition of plasmochin to the course of atabrine was widely diffused through the medical literature. This impression was fostered by the adoption at the outset of the present war of the so-called "2525"‡ regime by the Royal Army Medical Corps and the similar quinine-atabrine-plasmochin regime of the United States Army Medical Corps, so that it came as somewhat of a surprise to many when the Army treatment regimes were revised and plasmochin was dropped altogether. This gave plasmochin a bad name that it had certainly not earned, and led to such statements by the ill-informed as "Plasmochin has proved a failure" and "Plasmochin has not lived up to its reputation." The fact was that the Army authorities realized that there were few circumstances in which there was much to be gained by destroying the gametocytes whose destruction could in any case be achieved by a smaller dosage of plasmochin, that the antirelapse properties of this small dosage were at the best extremely slight in benign tertian and were nonexistent in malignant tertian infections and that it was not worth prolonging the treatment regime and risking toxic symptoms in the few persons who had an idiosyncrasy, for such questionable advantages. Plasmochin is still, however, the only drug that clears the blood of malignant tertian gametocytes¶ and in combination with other drugs prevents relapses in benign tertian malaria, or at least cuts them down to an extremely low percentage. One ought perhaps to return to the surer ground of the plasmochin-quinine combination and test the effect of a safe plasmochin dosage, that is, 0.01 gm. thrice daily, given coincidentally with quinine, over a longer period, say ten to fourteen days.

But this is not all. James and his co-workers[14] showed that by giving large doses of plasmochin (0.08 gm. daily for three days and 0.06 gm. for five, a total of 0.54 gm.) before and immediately after infection with benign tertian sporozoites, practical prophylaxis could be achieved, although they failed to produce this effect consistently with smaller, even though still toxic, doses, namely, 0.06 gm. daily for seven days. In the cases in which prophylaxis failed, the subjects had their first clinical attacks nine months after infection.

There is thus reason to believe that, although the practical use of plasmochin is limited by its high toxicity, it is in several ways a unique drug, in that it affects certain stages of both benign and malignant tertian parasites that are unaffected by the other antimalarial drugs now in use. It is hoped that, with plasmochin as an example, it will in time become possible to synthesize a quinolin derivative with the same therapeutic potentialities as plasmochin but without its limiting toxicity.

Quinine and Other Cinchona Alkaloids

Whereas the cinchona alkaloids have been in use for over three hundred years, the alkaloid quinine has occupied its special privileged position for less than a hundred years. The scientific basis for the choice of this alkaloid was probably sound, but the circumstances that placed it in such a position of dominance were unfortunate, for they led directly or indirectly to the development of a monopoly that had repercussions that have in turn proved disastrous to the outside world and to the monopolists themselves.

The climate in Java was such that it was possible to grow a particular variety of cinchona, *Cinchona ledgeriana*, which gave the richest yield of quinine, so much more easily than elsewhere that the large cinchona plantations in Ceylon, India, South America and elsewhere were eventually driven out

*Sinton and Bird[9] showed that when a course consisting of 0.10 gm. of plasmochin and 1.25 gm. of quinine daily for twenty-eight days was given to 20 soldiers with benign tertian malaria, no relapses occurred, and that when the dosage of plasmochin was reduced to 0.06 gm. daily in smaller subjects and the drugs were given for a total of seventeen days (with various intervals) to 15 soldiers, only three relapses occurred. That is, in 35 cases there were three relapses, a rate of 9 per cent, compared with a rate of 77 per cent in a series of 111 cases in which quinine was given in the usual doses. Sinton, Smith and Pottinger[9] also had no relapses in a series of 17 patients given 0.06 gm. plasmochin and 1.31 gm. of quinine for twenty-one days. All the subjects in these experiments and the controls were under military discipline and were kept under clinical and parasitologic observation for a minimum of two months; although this did not preclude the possibility of a late relapse, at least the controls showed a high percentage of relapses within these two months. In India, a course of 0.04 gm. of plasmochin and 1.31 gm. of quinine for three weeks was given to all soldiers, both British and Indian, with a benign tertian infection, with highly satisfactory results in a group of over 3000 cases — so satisfactory, in fact, that in 1934 the convalescent depot at Kasauli, where much important experimental work on antirelapse therapy had been done since 1924, had to be closed on account of the paucity of cases of relapsing benign tertian malaria. Since the fall in incidence preceded the adoption of atabrine, it was attributed by the Army authorities to plasmochin administration (Amy and Boyd[10]). Toxic effects were, however, not uncommon (Manifold[11]).

†In 1933–1934, Bird[12] in a series of trials in India showed that by giving 0.01 gm. thrice daily for five days after the course of atabrine, the relapse rate in benign tertian infection was reduced to 30 per cent, as against 45 per cent for quinine with the same plasmochin dosage; the groups comprised 150 and 200 cases, respectively. Gentzkow and Callender[13] also effected a distinct although not spectacular reduction in the recurrence rate among military personnel in Panama by adding 0.01 to 0.02 gm. of plasmochin to the atabrine course thrice daily for three to five days.

‡Two days of quinine, five days of atabrine, two days of rest and five days of plasmochin.

¶The closely allied Cilional, which has never been issued for general use, also achieves this but otherwise has no advantage over plasmochin, and so possibly do some of the other recently discovered drugs.

of business. The price of quinine was then raised to a level that made it difficult for the malaria sufferers in poor countries to afford the amounts of this drug that they needed.

It has long been appreciated that the other crystalline alkaloids of cinchona bark also have high antimalarial properties, and an attempt has been made in several countries to introduce a mixture of cinchona alkaloids — for example, the total crystalline alkaloids of the bark of certain hardier cinchona trees, *C. robusta* and *C. officinalis* — for general use against malaria. This scheme was fostered by the Health Organization of the League of Nations. The main obstacles to the more general adoption of the mixed alkaloids were the conservatism of the medical profession and the vested interests of the cinchona planters. The result was that when the Java plantations were taken by the Japanese early in 1942, little progress had been made in the scheme for extending the cinchona plantations in any of these countries. Nevertheless, it was believed that the possibilities should be further explored, and as a part of the research program further studies in the pharmacologic and therapeutic properties of the cinchona alkaloids were undertaken.

Pharmacology

As noted above, the peak plasma concentration of quinine is reached within four hours of the oral administration of this alkaloid, but the concentration falls rapidly. This means that it is a useful drug for its quick action but that continuous administration is essential for the action to be maintained. After the routine administration of quinine — 1.3 to 2.0 gm. daily in two or three doses — the plasma concentration reaches 3 to 10 mg. per liter and remains there.

The efficient therapeutic level varies for different hosts and for different species and strains of parasite; it is of the order of 3 to 5 mg. per liter but rises to 10 mg. for quinine-resistant strains, especially those of *P. falciparum*. It is, however, essential that this level be maintained for several days.

The rate of absorption and the levels of plasma concentration of quinidine and cinchonidine were found to be similar to those of quinine, but the rate of absorption of cinchonine appeared to be much slower and less complete. It was shown, however, that the absorption of cinchonine was actually as complete as that of quinine, but that its rate of degradation was much higher. As a result, the plasma level was only a fraction of that of quinine after the same oral or parenteral dose. On the other hand, the therapeutic activity of cinchonine was much greater than that of quinine, a plasma concentration of 0.3 mg. per liter maintained for four days being curative in benign tertian infections. The higher therapeutic activity of cinchonine thus fully compensates for the low plasma level, and the final result of the oral or parenteral administration of equal doses of the two drugs is the same, with perhaps a slight clinical advantage for cinchonine on account of its lower toxicity.

Clinical Experience

The Madras (India) Cinchona Commission in 1867–1868 first reported that the actions of the four principal cinchona alkaloids, quinine, quinidine, cinchonidine and cinchonine, on "malarial fever" were equal. This observation was confirmed later by several observers, including Sinton and Bird.[15] As a result of the renewed interest in this subject, further investigations were undertaken in the United States and Great Britain. All these confirmed the previous opinion that each of the other three crystalline alkaloids has approximately the same antimalarial action as has quinine. Field experiments also showed that a totaquine* mixture consisting of about 70 per cent total crystalline alkaloids was as effective as quinine alone in approximately the same dosage. It was, however, noted that the disagreeable by-effects were more frequent with totaquine, and it was once again concluded that these were mainly caused by the amorphous alkaloids in the mixture. On the other hand, there was no evidence that any one of the crystalline alkaloids or any combination of them was more effective than quinine in preventing relapses, or that any of them would act as a true causal prophylactic.

Since the peak plasma level is reached so soon, an initial loading of the dosage is unnecessary, and probably inadvisable, in the treatment of Asiatics of small stature with quinine or the other cinchona alkaloids, but for nonimmune white troops the Army practice is to give 1 gm. thrice daily for two days and 0.67 gm. thrice daily for the next five days. I believe that this is only to be recommended in malignant tertian infections.

As a suppressive drug, quinine was used extensively in World War I by the British and French in Macedonia. Its practical failure in this role was attributed to the failure to see that the troops took the drug properly, since for many years before and after 1918 it had been used extensively in civil life in the tropics, in some cases with a considerable degree of success. Since Pearl Harbor, not much quinine has been available for use as a suppressive, but on the few occasions on which it was used it was not a conspicuous success. Its pharmacology makes this understandable, and since there is no reason to believe that any of the other alkaloids would be more active, it seems probable that in this capacity the cinchona alkaloids will have to give way to one of the synthetic drugs, atabrine or its successor.

To summarize, recent experience in the laboratory and field has made no material difference in opinions concerning the value of quinine and the other cin-

*"Totaquina" is the name suggested by the Health Organization of the League of Nations for a standardized mixture of the alkaloids of cinchona; this is the official *B.P.* designation, the *U.S.P.* one being "totaquine."

chona crystalline alkaloids, although further scientific evidence has been provided to show that all the crystalline alkaloids of cinchona are equal in their antimalarial activity, and that a mixture of these alkaloids can be used as a completely efficient substitute for the single alkaloid quinine.

Other Synthetic Antimalarial Drugs

Another line of investigation has been the search for new synthetic antimalarial drugs. Many such drugs have been synthesized, and some have been shown to possess antimalarial properties equal to and even greater than that of atabrine, but their superiority has been quantitative rather than qualitative, and up to the present no one has been found that does what atabrine does not do, namely, destroy the sporozoites or prevent relapses in benign tertian malaria.

It is probable that if no better drug is found some of these will be manufactured and marketed after the war, but the authorities in the Allied countries have wisely decided that, in view of atabrine's background of fifteen years of laboratory and clinical trial, it would be foolish to change over to some other drug for the sake of apparent minor advantages, without the knowledge of its limitations that only long experience can provide.

Conclusions

Prior to 1942, atabrine was looked on as a valuable addition to the armamentarium of the physician for the cure and suppression of malaria, but its place was certainly second to that of quinine. Recent work has shown that it is probably the most valuable drug in the fight against malaria.

Despite the fact that quinine and the other cinchona alkaloids have had to take a place below atabrine on the antimalarial priority list, recent work has in no way questioned their efficacy. On the contrary, it has confirmed previous work regarding the antimalarial activity of all the crystalline alkaloids, and more especially that of a mixed alkaloidal preparation, which in some of the poorer malarious countries may, on economic grounds, still prove to be the drug of choice for the mass of the population.

The strict limitations of plasmochin in the treatment of malaria have long been recognized, and recent experience has merely served as a reminder of these limitations. It is, however, the only drug that acts as a true causal prophylactic or actually prevents relapses in benign tertian malaria, albeit in large and dangerous doses. These unique properties should be recognized and, in special circumstances, full advantage taken of them. Furthermore, it seems possible that by a modification of the formula of plasmochin a less toxic but equally efficacious drug may be synthesized. The discovery of such a drug will give man a weapon with which he will be able to control malaria not only in the individual but in the community. Although it is improbable that malaria will ever be banished by the use of drugs alone, with a drug possessing these properties it may be possible to control it in some communities where this was hitherto impossible, and in others to do so more effectively and at lower cost than would be possible by any other means. Until, however, such a drug is discovered no claim for man's mastery over malaria can be made.

It will be surprising if the intensive chemical and medical research that is now being carried on in several countries does not lead to the discovery of a synthetic drug in which all the qualities of the known antimalarial drugs are combined with some unique ones of its own. Meanwhile, there are three valuable antimalarial drugs: atabrine; the cinchona alkaloids, including quinine; and plasmochin. Each has its own place in the treatment of malaria.

References

1. Peter, F. M. Über die Wirkung des Atebrin gegen natürliche Malariainfektion. *Deutsche med. Wchnschr.* **58**:533-535, 1932.
2. Napier, L. E., and Das Gupta, B. M. Atebrin: synthetic drug for treatment of malaria. *Indian M. Gaz.* **67**:181-186, 1932.
3. Napier, L. E., Butcher, D., and Das Gupta, C. R. Field experiments with atebrin and plasmochin. *Indian M. Gaz.* **67**:186-191, 1932.
4. Green, R. Report on 50 cases of malaria treated with atebrin. *Lancet* **1**:826-829, 1932.
5. Shannon, J. A., Earle, D. P., Jr., Brodie, B. B., Taggart, J. V., and Berliner, R. W. Pharmacological basis for rational use of atabrine in treatment of malaria. *J. Pharmacol. & Exper. Therap.* **81**:307-330, 1944.
6. Green, R. A. Totaquine in treatment of malaria. *Bull. U. S. Army M. Dept.* No. 84, 51-57, 1945.
7. Roehl, W. Die Wirkung des Plasmochins auf die Vogelmalaria. *Arch. f. Schiffs- u. Tropen-Hyg.* **30** (supp.): 311, 1926.
8. Sinton, J. A., and Bird, W. Studies in malaria with special reference to treatment: plasmoquine in treatment of malaria. *Indian J. M. Research* **16**:159-177, 1928.
9. Sinton, J. A., Smith, S., and Pottinger, D. Studies in malaria, with special reference to treatment. XII. Further researches into treatment of chronic benign tertian malaria with plasmoquine and quinine. *Indian J. M. Research* **17**:793-814, 1930.
10. Amy, A. C., and Boyd, J. S. K. Malaria in India: synthetic drugs and relapse rate. *J. Roy. Army M. Corps* **67**:1, 1936.
11. Manifold, J. A. Report on trial of plasmoquine and quinine in treatment of benign tertian malaria. *J. Roy. Army M. Corps* **56**:321 and 410, 1931.
12. Bird, W. Atebrin and plasmoquine in treatment of benign tertian malaria. *J. Mal. Inst. India* **5**:395, 1944.
13. Gentzkow, C. J., and Callender, G. R. Malaria in Panama Canal Department, United States Army: results of treatment with quinine, atabrine and plasmochin. *Am. J. Hyg.* **28**:174-189, 1938.
14. Third general report of Malaria Commission. *Quart. Bull. Health Organ. League of Nations* **2**:181, 1931.
15. Sinton, J. A., and Bird, W. Studies in malaria, with special reference to treatment. XI. Cinchona alkaloids in treatment of benign tertian malaria. *Indian J. M. Research* **16**:725-746, 1929.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
EDITH E. PARRIS, *Assistant Editor*

CASE 31281

PRESENTATION OF CASE

A forty-five-year-old hospital attendant was admitted because of an increasingly productive cough.

About one and a half years before admission the patient began to notice painless swelling of the finger tips and stiffness in the knees. The limitation of motion slowly progressed to involve the ankles, wrists, elbows and interphalangeal joints of the hands and feet. These joints were never red or hot. The stiffness was accompanied by dull constant pain, which diminished somewhat with use. Gradually the involvement of the upper extremities subsided, but the knees and ankles became very swollen and exquisitely painful and the limitation of motion progressed. There was still no redness or heat. Two months before admission he was advised to have his remaining teeth extracted. This he had done. About a month before entry, without chills, fever or chest pain, he developed a productive cough, which soon daily yielded 200 to 400 cc. of whitish, non-blood-streaked phlegm. He also began to have night sweats two or three times a week. During the nine months before admission he had complained of dyspnea on exertion, which did not progress. His appetite had remained good, but during the previous one and a half years he had lost 15 pounds.

There was no history of gonorrhea or exposure to tuberculosis. For many years the patient had imbibed freely of rum.

Physical examination revealed an emaciated, moderately dyspneic, edentulous man in considerable discomfort because of painful legs. He showed definite gynecomastia. Expansion of the chest was symmetrical, and the chest appeared to be fairly emphysematous. Rhonchi and wheezes were heard over the entire chest posteriorly but were most pronounced at the bases. Tactile and vocal fremitus and resonance were normal. The abdominal wall showed considerably dilated veins. The liver and spleen were not enlarged. The knees, ankles, feet and all toes showed marked swelling, tenderness and pain on motion. The skin over these areas was tense, glossy and light pink. There was no redness or heat but marked hyperhidrosis. The patellas were definitely elevated and ballotable, and a fluid wave could be obtained over the knee joints. The swelling over the legs, ankles and dorsums of the feet was firm and did not pit. The fingers and toes showed clubbing of an advanced degree.

The temperature was 99.5°F., the pulse 90, and the respirations 20. The blood pressure was 112 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 4,700,000, with 11 gm. of hemoglobin, and a white-cell count of 10,500, with 77 per cent neutrophils. The urine was normal. The serum chloride was 95 milliequiv. per liter, the prothrombin time 22 seconds (normal, 18 to 20 seconds), the protein 4.8 gm. per 100 cc., the calcium 6.6 to 8.3 mg. per 100 cc., the phosphorus 3.1 mg., the cephalin flocculation test + in forty-eight hours, the alkaline phosphatase 4.1 units per 100 cc., and the corrected sedimentation rate 1.7 mm. per minute. The stool was normal. Synovial fluid drawn from the left knee was slightly cloudy and pale yellow, and most of it promptly clotted. It contained 100 white cells and 700 red cells per cubic millimeter (of the former, 20 per cent were polymorphonuclear cells and 80 per cent were monocytes) and 106 mg. of sugar (serum sugar 136 mg.) and 2.2 gm. of protein per 100 cc. Repeated sputum cultures showed few beta-hemolytic streptococci, a few staphylococci and no pneumococci, spirochetes or other pathogens of significance. The Hinton test was negative. A 1:10,000 tuberculin test showed a 1.0-cm. area of redness with a 0.5-cm. central zone of induration. A bronchoscopic examination was negative, except for the presence of an increased amount of thin white secretion.

X-ray studies showed slight decalcification of the bones of the hands, arms, knees and feet. There was an extensive feathery periosteal proliferation involving the majority of the bones. This had the characteristic appearance of pulmonary osteoarthropathy. The chest films showed a homogeneous shadow of increased density with somewhat ill-defined margins in the axillary portion of the left upper lobe. No definite fluid level was seen. The diaphragm, heart and aorta appeared normal.

Throughout the patient's course in the hospital the temperature was normal except for an occasional low-grade fever, which rarely reached 101°F. The pulse was somewhat elevated, usually between 90 and 110, and the respirations were normal. He produced from 60 to 400 cc. of white nonpurulent sputum daily. His appetite remained fair, and he lost no further weight.

After the second week he was given approximately 100,000 units of penicillin per day. Aspirin fairly well controlled his joint discomfort. A cephalin flocculation test repeated during the third week was +++ in forty-eight hours. The prothrombin time was 31 seconds (normal, 18 to 20 seconds). During the fifth week the calcium was 8.3 mg. per 100 cc. and the protein 6.0 gm. per 100 cc. X-ray films of the chest repeated four and six weeks after ad-

*On leave of absence.

mission showed a rather marked increase in the size of the lesion in the left upper lobe on each occasion (Fig. 1). The patient insisted that his joints were less painful and that he felt generally better. The urine remained normal, except for a ++ test for urinary calcium (Sulkowitch test). The white-cell count rose briefly to 23,800, with 83 per cent neutrophils.

He was given several whole-blood transfusions and was maintained on daily penicillin, Synokovite and Hykinone for two weeks. On the thirty-first hospital day an operation was performed.

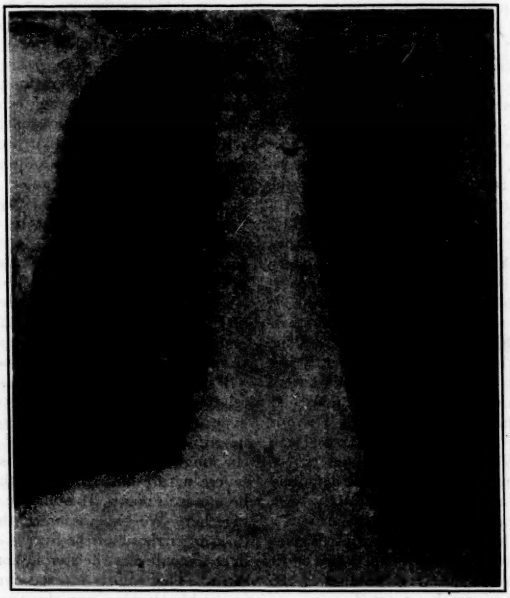

FIGURE 1. *Roentgenogram of Chest.*

DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: One point in the history worth commenting on is that the patient noticed painless swelling of the finger tips one and a half years before entry. If that is an accurate observation, then we can date the beginning of clubbed fingers. It is not infrequent, however, for a patient to mistake the terminal joint for the tip of the finger, so that the patient's statement, unless he was sure of it, may be a source of error. I shall assume, however, that he had clubbed fingers beginning one and a half years ago.

The symptoms and signs in this case center around three systems — the lungs, the liver and the joints. It would be nice if we could find a diagnosis to cover all three systems. The chances are that we shall not be able to. We might rule out some diagnoses right away and include others. I think one can rule out pulmonary tuberculosis simply because the x-ray appearance is not characteristic and because the negative sputum and the past history are against it. The patient undoubtedly had pulmonary osteoarthropathy. That diagnosis is given to us. It was an extensive type of pulmonary osteoarthropathy. He certainly had some form of liver disease. He had a high alcoholic intake, dilated abdominal veins and gynecomastia, which are important in the diagnosis of liver disease. The blood chemistry is also consistent with liver disease. The prothrombin time was elevated, the serum protein was low, and the cephalin flocculation test was positive. We presume that they looked carefully for varices of the esophagus, which were not found, unless they were so sure of the diagnosis that they deemed it unnecessary to look. We may conclude that he had characteristic portal cirrhosis.

As so often happens in these cases with long-standing pulmonary disease associated with liver

disease one has to include amyloid disease in the differential diagnosis. There is, however, a good deal of evidence against amyloid disease. In the first place, the liver and spleen were not enlarged. Enlargement of these organs is a common finding in amyloid disease. Furthermore, there is no mention of the Congo red test. If it had been done I assume that it was negative. If it had not been done then certainly they did not think much of this diagnosis. My first impression in reading the story was that this patient did not have amyloid disease.

Could he have had rheumatoid arthritis? The history is consistent with this diagnosis except for the onset of clubbed fingers one and a half years previously. I am inclined to believe that the joint symptoms were part of the picture of chronic pulmonary osteoarthropathy rather than ordinary rheumatoid arthritis. As to the nature of the lung condition itself, before we go farther, I should like to see the x-ray films, particularly those of the lungs.

DR. GEORGE W. HOLMES: The changes in the periosteum are well marked and extensive. It is a characteristic picture. I believe that one can say, so far as one can see on the x-ray films alone, that the whole picture in the joints was due to pulmonary osteoarthropathy. There is no evidence of rheumatoid arthritis. The joint spaces are not narrowed. If he had had rheumatoid arthritis for one and a half years there should be more evidence in these films.

In the chest there is a lesion that apparently lies outside the bronchus. It does not seem to interfere with the passage of air through the bronchi because the lungs and diaphragm move normally. There is no mediastinal shift. Furthermore, so far as I can make out, there are no metastatic masses or enlarged hilar lymph nodes. The lesion is definitely lobulated and the margins are not distinctly seen, but there is no cavity. It is possible, even with a homogeneous picture like this, that the cavity is completely filled with fluid. I presume that every effort was made to demonstrate a cavity because of the history of having had his teeth extracted.

We have no evidence that the bronchus is obstructed. The location of the tumor is of some interest. Apparently it is in the midportion of the chest, within the lung. It does not seem to reach the pleura, except at this point. Of course it would be helpful if I could tell you whether it is benign or malignant, and if the latter, whether it is primary or metastatic; but I cannot.

DR. LERMAN: Dr. Holmes has been of help in one respect. He agrees that there is no rheumatoid arthritis and that this part of the picture is part of the syndrome of pulmonary osteoarthropathy.

What is the possibility of pulmonary suppuration? The patient had symptoms following the extraction of teeth but did not have chills or fever, and the chest films did not reveal an abscess cavity. Consequently we do not have sufficient evidence to make a diagnosis of lung abscess. Moreover, the pulmonary osteoarthropathy in all probability antedated the development of the pulmonary symptoms. I think one may say that pulmonary abscess does not play an important role here unless there was an abscess caused by the breakdown of a tumor. Similarly we can discard an encapsulated empyema. There is no previous history of pulmonary infection, nor did this process displace the mediastinal contents as it progressed. Certainly the patient did not have the characteristic chills and fever and was not so sick as one would expect him to be with an encapsulated empyema.

The major problem is to decide whether this was a benign or malignant tumor. The presence of chronic pulmonary osteoarthropathy of an extensive sort favors a malignant tumor of the lung rather than a benign one, although I have seen one patient with an adenoma of the bronchus who had an extensive pulmonary osteoarthropathy. The rapid spread during the course of observation favors the diagnosis of malignant tumor. The long duration of pulmonary osteoarthropathy does not rule out malignancy but merely means that the tumor was of a slowly growing type. It is somewhat unusual for a malignant tumor not to show by x-ray some evidence of its character. I should say that, by and large, bronchoscopy should have revealed something of the nature and origin of this tumor if it were malignant unless it was in such an awkward position that the bronchoscopist could not see it.

I should like to digress a moment to discuss the relation between malignant tumor of the lung, gynecomastia and osteoarthropathy. There are descriptions in the literature of malignant tumor of the lung, chronic pulmonary osteoarthropathy of a severe nature and gynecomastia. This happens to be a case in point. It would be nice to put them all together. We have assumed that gynecomastia in cases of cirrhosis of the liver is due to failure of the liver to conjugate the steroid hormones, particularly estrin. This results in excessive amounts of estrin in the blood. One may theorize further that excess estrin, or some other steroid, may reach the terminal portions of the bones and produce changes in the periosteum characteristic of pulmonary osteoarthropathy. We know that these steroids have definite actions on the calcium metabolism and on the deposition of matrix in the bone. Failure to neutralize the steroid hormones might explain clubbing in cases in which some form of liver disease is present, but what about those that do not have obvious liver disease? One possible assumption in these cases is that malignant tumors of the lung frequently develop necrosis and suppuration, which may produce amyloid changes in the liver and simulate the functional disturbance present in cirrhosis. I merely interject this as a possible explanation. At grand rounds this morning a patient of Dr. Chester M. Jones was presented who had pulmonary osteoarthropathy and diarrhea, the latter probably

associated with a deficiency state. Here again is an ideal setup for liver disease and the development of pulmonary osteoarthropathy on the basis of the mechanism just proposed. It would be valuable support for this theory if Dr. Jones's patient had gynecomastia, but unfortunately he does not.

DR. BENJAMIN CASTLEMAN: The twenty-four-hour excretion of 17-ketosteroids was 7.6 mg. corrected and 8.6 mg. uncorrected.

DR. LERMAN: That is a normal range for a patient who is sick. This test does not tell us about the excretion of other steroids, particularly estrin.

Unfortunately there is no easy test for estrin compounds. It necessitates a good deal of biologic testing and little of it is done. Nor is there an easy test for the progestin compounds, which may be present in male urine.

The second question is whether this was a primary or a metastatic lesion. One might speculate on the possibility of a metastatic lesion from the liver. We know that the patient had cirrhosis, and portal cirrhosis is frequently a precursor of hepatoma. This might, therefore, be a metastatic lesion from the liver. There is, however, no mention in the record of an abnormal mass in the liver. The liver was not palpable. This is against the diagnosis of hepatoma. Moreover, it seems unlikely that a secondary lesion from the liver could have gone on for a year and a half without producing evidence of metastatic lesions elsewhere in the body. It is an unlikely but a plausible way of tying in all three systems.

I believe that this patient had a malignant lesion of the lung, most likely a carcinoma but possibly some form of sarcoma, associated with pulmonary osteoarthropathy of long standing, and an independent portal cirrhosis.

DR. RICHARD H. SWEET: The findings at operation are often of much less importance than the necessity for making an accurate preoperative diagnosis. This case was presented to me as one of lung abscess. I did not accept that diagnosis, but I should like to point out the importance of making sure.

This man was in such poor condition that I was in no haste to operate. It took a good deal of prodding on the part of the house staff to get me to consent to operate at all. You can readily see that in a patient in such poor condition it is essential to determine the type of procedure beforehand; if it were an abscess one could do nothing but make an incision and drain, whereas if it were carcinoma one would do an open exploration. I throw that in for what it is worth. I came to the conclusion, as Dr. Lerman did, that it was carcinoma, and used the extreme degree of pulmonary osteoarthropathy in making the diagnosis. We performed a total pneumonectomy.

CLINICAL DIAGNOSES

Carcinoma of lung.
Pulmonary osteoarthropathy.

DR. LERMAN'S DIAGNOSES

Malignant tumor of lung, probably carcinoma.
Pulmonary osteoarthropathy, chronic.
Portal cirrhosis.

ANATOMICAL DIAGNOSES

Adenocarcinoma of lung.
Pulmonary osteoarthropathy, severe.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This was a large granular tumor through which many small bronchi traversed (Fig. 2). There was, however, no obstruction to the large

FIGURE 2. *Photograph of Cross Section of Resected Left Lung.*

bronchi, although one of the bronchi in the posterolateral segment of the upper lobe did contain a nodule eroding the mucosa, which suggests a bronchiogenic origin. It is interesting to note that the tumor crossed the septum and extended for a short distance into the apex of the lower lobe. Microscopically the tumor turned out to be a low-grade adenocarcinoma. We have found that adenocarcinoma of the lung rarely occurs at the hilus, as in this case, usually being located more peripherally than are the epidermoid and oat-cell cancers. There was also a small metastasis in the lower lobe.

This man died soon after operation, and at autopsy we found a large metastasis in one of the adrenal glands. The sections of the breast showed a rather extreme degree of gynecomastia. In this

connection Fried* has reported 4 cases of carcinoma of the lung with pulmonary osteoarthropathy and some endocrine disturbance, such as gynecomastia. He also found that in some of these cases the anterior portion of the pituitary gland was increased in size, and in some the eosinophilic cells were increased in number. In this case, however, the pituitary gland was of normal size, and although I did not really count the cells, there did not seem to be an increase in the number of eosinophilic cells.

DR. LERMAN: How about the liver?

DR. CASTLEMAN: There was no cirrhosis or any evidence of chronic disease. There was some central congestion and necrosis, which was probably terminal.

DR. MARIAN W. ROPES: It is surprising how many patients with pulmonary osteoarthropathy come in with a diagnosis of rheumatoid arthritis.

DR. CASTLEMAN: We examined some of the bones microscopically and found all stages of periostitis — from the radiating fibrillar strands out from the cambium or inner periosteal layer to osteoid formation and, finally, calcification and fusion with the cortex.

*Fried, B. M. Chronic pulmonary osteoarthropathy: dyspituitarism as probable cause. *Arch. Int. Med.* 72:565–580, 1943.

CASE 31282

PRESENTATION OF CASE

A sixty-seven-year-old, invalid woman was admitted to the Emergency Ward at midnight because of hematemesis.

About six years before admission the patient had an episode of severe hematemesis, and about four months before entry she had another. On both occasions she was admitted to a hospital and carefully examined. The source of the hemorrhages could not be discovered. Four hours before admission to this hospital she had vomited a large amount of bright-red blood with clots. She became weak and apprehensive. A physician gave her a "hypodermic." Three hours later she came to the hospital. She had had rheumatoid arthritis for many years, and for the past eighteen years had been completely confined to a chair-and-bed existence. In addition to the above-mentioned hematemesis she had had other episodes of vomiting small amounts of blood. She had had no epigastric distress at any time and had never noted tarry stools. For many years she had taken an occasional aspirin tablet, which caused no gastric discomfort. There had been no awareness of fever. During the previous six months she had become somewhat anorexic. She had lost a great deal of weight and had noted a gradual increase in the size of her abdomen. She developed a bedsore on the back about four months before entry and had also noticed occasional burning on urination and occasional incontinence of urine.

Eighteen years before entry she had had all her teeth extracted. For years she had had hemorrhoids, which bled frequently.

Physical examination revealed an emaciated, pale, grossly deformed woman with stertorous breathing and in a clouded mental state. There was bright-red blood about the lips. The tongue was not atrophic, but there were a few varices along the edges. The skin was loose, thin and extremely pale. The scleras were white. There were severe flexion deformities of the joints, all the large joints except the hips being rigidly ankylosed. Fine and moist basal rales were heard over both sides of the chest, and diffuse wheezes over the entire chest posteriorly. The heart was normal. The aortic second sound was greater than the pulmonic. The abdomen was distended and contained a moderate amount of fluid. The liver and spleen were not felt. A deep decubitus ulcer lay over the sacrum.

The temperature was 97°F., the pulse 100, and the respirations 15. The blood pressure was 125 systolic, 65 diastolic.

Examination of the blood showed a red-cell count of 2,300,000, with 7 gm. of hemoglobin, and a white-cell count of 11,500, with 95 per cent neutrophils. The urine was acid, with a specific gravity of 1.018; the sediment contained innumerable white cells, an occasional red cell and many bacteria. The stool was liquid and grossly bloody. The serum nonprotein nitrogen was 27 mg. per 100 cc., the fasting blood sugar 133 mg., the carbon dioxide 21.2 milliequiv. per liter, and the prothrombin time 17 seconds (normal, 18 to 20 seconds). A urine culture showed abundant growth of *Proteus vulgaris*.

A whole blood transfusion was begun shortly after admission. At 9:00 a.m. she was responsive and recognized her friends. She had not vomited since admission and showed no other signs of active bleeding. At 3:30 p.m. on the first day the blood pressure had fallen to 80 systolic, 40 diastolic, and the pulse had risen to 130. The skin was cool and clammy, and the patient was disoriented. At about 11:00 p.m. on that day, after a low enema, she passed a large quantity of fresh and clotted blood by rectum. At 9:30 a.m. on the second day the blood pressure had returned to 110 systolic, 70 diastolic, and the pulse was 110. She was in profound coma, and the respirations were stertorous. There were coarse gurgling rales in the dependent part of the chest. The pulse became progressively more rapid and thready. At noon on the second day she vomited dark-red blood. The hemoglobin level at that time was 4 gm. per 100 cc. She expired at 3:00 p. m.

DIFFERENTIAL DIAGNOSIS

DR. CHESTER M. JONES: We are not favored by x-ray films in this case, and I do not know whether or not that is going to be a help to me. I have been

making notes and juggling figures wondering how I shall bet, but I am definitely far from certain. In regard to the varices, were they said to be telangiectases in the record?

DR. BENJAMIN CASTLEMAN: Dr. Pittman, can you answer that?

DR. HELEN S. PITTMAN: As I recall they were definitely dilated superficial vessels, not telangiectases.

DR. JONES: I believe that this patient had more than one disease, which is not at all infrequent in this age group. She had obviously had rheumatoid arthritis for many years. Many patients with rheumatoid arthritis are badly nourished, however, as a result of anorexia and loss of weight. Nutritional disturbances, such as hypoproteinemia, prolonged prothrombin time and so forth, are not rare, particularly if salicylates have been given. Furthermore, as our group here has seen, rheumatoid arthritis may be accompanied by changes in the liver, including those of amyloidosis. But it is difficult to see how this could precipitate a picture such as this woman showed. It seems to me that the rheumatoid arthritis is not of primary importance.

The patient gave a six-year story of vomiting, off and on, with two major hemorrhages and a certain number of minor hemorrhages before her final admission. She had no other symptoms of any sort until six months before she entered. At that time she had a different story, namely, one of an increasing loss of appetite and a gradual swelling of the belly, accompanied by marked loss of weight; in other words, there was more weight loss than the scales showed. There was compensation, in a sense, because of an accumulation of fluid in the abdominal cavity. It seems to me that we have to explain the repeated hematemeses and the recent ascites, for both of which we have evidence on physical examination as well as from the story.

What are the causes of vomiting blood from the upper gastrointestinal tract? They are all perfectly well known. It is just a question of which one of these fits the picture, particularly if we try to tie in the ascites. If she had an ulcer, it should have been picked up on one of the previous x-ray examinations. She had had two gastrointestinal series, which at least were said to have been done carefully, — the first one six years before entry, and the second one four years before entry, — and no ulcer was noted. The absence of an ulcer story, together with the failure to find an ulcer by x-ray examination after a careful search, is definite evidence against such a diagnosis, although it does not rule it out. We have had more than one case of a bleeding ulcer that was not found until demonstrated by autopsy or operation, but that is the exception. In these exercises, the proper thing to do is to try to make a logical diagnosis on the basis of the facts presented. I believe that duodenal, gastric or esophageal ulcer is unlikely.

Could she have had esophageal varices, secondary to cirrhosis of the liver and causing bleeding and ascites? If one asks the question that way, of course the answer is that she could have had them; but with such a diagnosis, it would be unusual for her to have lived six years after the first hemorrhage. In the younger age group, we do encounter repeated hemorrhages from esophageal varices due to portal hypertension, the so-called "Banti syndrome"; but in the older group, it is unusual to have a six-year interval between the first hemorrhage and the final fatal hemorrhage. I think this is of some importance in an attempt to rule out esophageal varices based on cirrhosis. Incidentally, it looks as if I were talking myself right into a corner. She was x-rayed at another hospital four months before, and if she had had varices they would undoubtedly have been spotted at that time. I assume that nothing was found.

DR. CASTLEMAN: The only statement that we have with reference to the hospital visit four months ago is that the daughter said that no cause was found for the vomiting of blood.

DR. JONES: Esophageal varices that cause hemorrhage can occasionally be missed by a careful roentgenologist, but with the six-year story of bleeding it seems rather unlikely that they would have been missed if they had been looked for. At times they are not found simply because the x-ray examination is done in a routine fashion and the esophagus not studied, only the stomach and duodenum being examined as the possible sources of the bleeding. She did not have a palpable spleen or liver, but I think that this may have been because the abdomen was so distended that it was impossible to feel a slightly enlarged spleen or liver. At any rate, for the time being I think that we have to pigeonhole a diagnosis of cirrhosis, but I am sure that it cannot be ruled out.

We have next to consider carcinoma. As a cause of the hemorrhage six years previously this also is an unlikely diagnosis. It is possible, however, that she had carcinoma of the stomach secondary to a benign polyp. We have seen that combination occasionally, but it is an unusual clinical picture. A polyp of the stomach is notoriously silent, and it can be missed by x-ray examination, since it is sometimes difficult to see. Subsequently the polyp may become malignant. Could that account for the ascites? It could, if by that time the patient had a carcinomatous process that had gone through the serosa of the stomach, or if there were regional metastases, either to the lymph nodes or to the liver. So I believe that that has to be put down as a possibility.

Diaphragmatic hernia could perfectly well account for the bleeding, although she had had no symptoms suggestive of diaphragmatic hernia. One sometimes sees fatal hemorrhage from diaphragmatic hernia in old people, but usually there

are symptoms suggesting something around the esophagus or stomach. Furthermore, x-ray films had been taken recently, and they should have shown a diaphragmatic hernia if it had been present. Again, this diagnosis can be missed in routine x-ray studies, but I should think that, if a hernia had been the cause of the hemorrhage, it would have been a fairly large one and would have been noted on x-ray examination.

One thinks of gastritis as a possible cause for this picture, although there were no symptoms. When gastritis is the major cause of hemorrhage, symptoms usually accompany it. With malnutrition, it is not at all surprising to get changes in the gastric mucosa and some atrophy, but this does not imply that such changes were the cause of this patient's bleeding. There is one theoretical reason for gastritis that might be considered, namely, the administration of aspirin. The record states that the patient took an occasional aspirin tablet. If she had been given a dosage of aspirin as large as that frequently employed in this hospital for painful rheumatoid arthritis, one could properly consider the question of gastritis. Fatal hemorrhage from this source has been noted in isolated cases, but it is most unusual to have repeated hemorrhages for six years on the basis of a gastritis due to aspirin. Furthermore, I believe that if this were so there would be a note in the record stating that the patient had taken a lot of aspirin and that it had been discontinued. Symptoms would probably be noted as well. I doubt that the aspirin plays any great role in this case.

If we consider only these five possibilities, we still have no conclusive evidence to help make a diagnosis. There are other conceivable conditions, and I suppose that they might as well be mentioned. She might have had a telangiectasis of the stomach, a curious congenital type of disease that may result in repeated hemorrhages over a long period of time. The telangiectases may be in the mouth, in the gastric mucosa or in any other part of the digestive tract. I take it that the lesions on the tongue were not the type that one gets in multiple telangiectases. I do not believe that she had it.

She could have had abdominal apoplexy, in the sense that one may get massive hemorrhage from a slight erosion that is not caused by a typical peptic ulcer, in which event this hemorrhage may occur anywhere in the gastrointestinal tract and all the x-ray films may be negative. Usually, however, there are a local source of irritation, specific pain and a marked rise in pressure that produces massive hemorrhage. There is no evidence that this patient had hypertension of any degree, so there is no reason to assume that such a thing occurred.

The case boils down, then, to the consideration of ulcer, esophageal varices, cancer on the basis of preceding polyp, diaphragmatic hernia and gastritis, as the only reasonable possibilities. It is fair to say that the ascites could have been on the basis of nutritional edema. One sees such a picture occasionally, and one is hard put to explain why it occurs only in the abdomen and not in the extremities. We know that the patient had malnutrition. The aspirin may be a red herring. The ascites could have been on the basis of cirrhosis of the liver or on the basis of carcinomatosis, with the primary focus in the stomach or possibly in the duodenum. It seems to me that when forced to choose between such possibilities I am inclined to select cancer on the basis of a previous polyp of the stomach, in large part because of the story of definite loss of appetite of six months' duration, obviously a new symptom for her since she talked about it. Apparently this represented a striking change, something more than rheumatoid arthritis. I believe that this is the most logical bet. If she had cancer, she may or may not have had metastases. She could perfectly well have had fluid in the abdomen due only to malnutrition, although the normal prothrombin time is definitely against it; it is likelier that there were metastases. The other possibilities are cirrhosis with esophageal varices, a silent ulcer and gastritis. I do not see how I can make a more logical explanation. To the best of my knowledge I have never seen ascites associated with a single hemorrhage from ulcer.

DR. PITTMAN: We did not believe that it was possible for anyone to make a definite diagnosis on this woman, or at least, I did not believe that it was. She was moribund when she came in, and her daughter added little to the history. I thought, as reported on the record, that a malignant neoplasm was likelier than cirrhosis. The resident bet on cirrhosis with esophageal varices, because he had been impressed with the fact that liver disease does occur in long-standing arthritis.

DR. MARIAN W. ROPES: The impression that cirrhosis commonly occurs in arthritis is due to the fact that we recently had several patients with this combination. In general, the only evidence that we have comprises minimal changes in liver function in a fairly large number of cases.

CLINICAL DIAGNOSES

Cancer of stomach.
Cirrhosis of liver, with esophageal varices?
Rheumatoid arthritis, chronic.

DR. JONES'S DIAGNOSES

Carcinoma of stomach, secondary to polyp.
Rheumatoid arthritis, chronic.

Anatomical Diagnoses

Portal cirrhosis of liver, with ruptured esophageal and gastric varices.
Hemorrhage into gastrointestinal tract.
Ascites.
Rheumatoid arthritis, chronic.

Pathological Discussion

Dr. Castleman: The autopsy showed an atrophic, cirrhotic liver, weighing 1000 gm. Microscopically it appeared just like the ordinary garden variety of portal cirrhosis. The process was healed, showing a lot of scarring and surrounding areas of regeneration. The spleen was enlarged, weighing 500 gm. She was a small woman, and probably the reason the spleen could not be felt was that there was 2000 cc. of ascitic fluid. The lower three fourths of the esophagus and the first 3 or 4 cm. of the stomach contained huge distended veins, and although we could not find the exact bleeding point at the time of autopsy, which is often the rule because it usually seals over, there is no doubt that a ruptured varix was the source of the hemorrhage. The entire gastrointestinal tract was filled with blood.

Dr. Jones: Which were larger, the esophageal or the gastric veins? The reason I ask is that I am sure that the x-ray examination four months before entry was not a careful one.

Dr. Pittman: I do not believe that she ever had a careful x-ray examination. She was terribly bent over and crippled by the arthritis, and it is dubious that she could have had an adequate gastrointestinal x-ray study.

Dr. Jones: We have seen bleeding from gastric varices on few occasions, sometimes due to portal hypertension associated with cirrhosis of the liver or disease of the spleen and splenic vein.

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POSTGRADUATE TRAINING OF MEDICAL OFFICERS

During 1944, questionnaires requesting information concerning their wishes regarding future medical training were mailed to the approximately 60,000 medical officers on duty with the Army, Navy, Public Health Service and Veterans' Administration. The information contained in the questionnaires returned by 21,029 medical officers is analyzed in the final report,* and the resulting figures present a challenge to all organizations that are considering programs designed to meet the educational requirements of the discharged medical officer. Furthermore, the analysis indicates that certification by a specialty board is the ultimate goal of the young physician — a trend that may materially alter methods for the practice of medicine in the immediate future.

The percentages of officers expressing a desire for long (six or more months) and short (less than six months) courses of instruction were 59.6 and 21.7, respectively, the remainder stating that they did not want any future training.

The ten most popular subjects for the long courses were, in order of frequency, as follows: surgery, internal medicine, obstetrics and gynecology, general review, psychiatry and neurology, pediatrics, orthopedic surgery, ophthalmology, radiology and otolaryngology. The corresponding topics for the short courses were as follows: internal medicine, surgery, general review, obstetrics and gynecology, pediatrics, otolaryngology, ophthalmology, psychiatry and neurology, radiology and orthopedic surgery.

Sixty-three per cent of the group stated that they wished to become certified specialists, and nearly 16 per cent had already been certified by one of the specialty boards. This is all the more surprising when it is learned that nearly 40 per cent of these medical officers had entered military service from private practice.

If one applies the percentages of those desiring long and short courses of instruction to the approximately 60,000 medical officers on active duty, one obtains the figures of 35,800 and 13,000, respectively. Such numbers are sure to tax, if not overwhelm, any scheme of postgraduate instruction that might be devised. It is possible that the eventual figures will not be so large and that the times of discharge will be so staggered that the full impact will be avoided, but in any case, all agencies concerned with supplying these educational facilities — medical schools, hospitals and national, state and local medical societies — should be actively devising methods to meet the demand. This is particularly imperative because of the shortage of medical-school graduates that is bound to occur within the next few years, owing to the shortsighted regulations regarding deferment.

The fact that nearly 80 per cent of this group of relatively young physicians are either certified or

*Lueth, H. C. Postgraduate wishes of medical officers: final report on 21,029 questionnaires. *J. A. M. A.* **127**:759-770, 1945.

desire to become certified by one of the specialty boards is difficult to evaluate. Certainly the practice of medicine has not reached the point — and probably never will — where 20 per cent of the licensed physicians can care for the ordinary aches and pains of the population; indeed, a reverse of the figures appears to be more accurate. Undoubtedly the need for certified specialists is constantly increasing as the science of medicine advances, but the general practitioner must still serve, particularly in small cities, towns and rural districts, unless, perhaps, medical practice is to be radically altered.

PENICILLIN AND SYPHILIS: A WARNING

PENICILLIN has been used in the treatment of syphilis in various stages and has been found effective in clearing up the manifestations of the disease. Stokes,[1] in discussing the treatment of late syphilis with penicillin, states that it produces symptomatic and serologic transformations that are equal if not superior to those obtained by long and arduous procedures with arsenic and heavy metals. Moore[2] reviews the history of chemotherapy and concludes, "The rapid and safe cure of early syphilis is just around the corner." He qualifies this statement, however, as follows: "How best to use it [penicillin], alone or in combination with other forms of treatment, is as yet undetermined but is under organized nation-wide, governmentally sponsored study, from which definite results may be expected rapidly to emerge." This new form of therapy has spurred investigation into other rapid methods of treatment, employing large and frequent doses of agents heretofore used. Although the reports of results by all these methods are distinctly encouraging it should be remembered that the determination of the ultimate cure of syphilis is a long-range process measured in years rather than in months. The ability of the *Treponema pallidum* to remain dormant for many years and even affect the second generation many years after birth has been demonstrated all too frequently in the past.

With these tragedies in mind it is well to mix a word of caution with enthusiasm for a new method of treatment until the end-results are definitely known. It is therefore of special importance that all patients treated for syphilis in this interim of determining the proper and infallible method, if such can be found, should be followed up serologically and physically with great care over a period of years. Every returning veteran who has been given penicillin for syphilis should therefore be re-examined from time to time to prevent, so far as possible, the late ravages of the disease in himself and his family.

REFERENCES

1. Stokes, J. H. Penicillin in late syphilis: interim report. *Am. J. Syph., Gonor. & Ven. Dis.* **29**:313-333, 1945.
2. Moore, J. E. Chemotherapy of syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **29**:185-199, 1945.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GREENWAY — Major Thomas H. Greenway, A.U.S., formerly of Three Rivers, died June 23 at the Cushing General Hospital, Framingham. He was in his forty-fifth year.

Dr. Greenway received his degree from Tufts College Medical School in 1927 and for a time maintained offices in both Three Rivers and Palmer. He served for a number of years as a member of the board of health and as associate medical examiner for this district. Shortly after entering the Army, in June, 1942, he was sent to the South Pacific as medical officer with an amphibious engineers' unit. At [redacted] he was named for conspicuous heroism when, after being buried under the debris of a falling building, he dug himself out and continued to direct under enemy fire the care of the wounded. After being hospitalized in Australia for a severe case of malaria, he returned to active duty and, while participating in landing operations in an island invasion, received an injury to his back, which resulted in his return to this country for treatment. He was a member of the staff of the Wing Memorial Hospital, Palmer.

His parents, his widow, two daughters, a son and four sisters survive.

PATTERSON — Alice M. Patterson, M.D., of Marblehead, died June 20. She was in her seventy-sixth year.

Dr. Patterson received her degree from Tufts College Medical School in 1904.

TRUESDALE — Philemon E. Truesdale, M.D., of Fall River, died June 12. He was in his seventy-first year.

Dr. Truesdale received his degree from Harvard Medical School in 1898. He joined the medical corps of the United States Army in 1917 and sailed for France with the rank of captain in the Yale Mobile Hospital Unit. In October, 1918, he was promoted to the rank of major. On his return to the United States he was assigned as director of surgery at Camp Devens and honorably discharged on March 15, 1919. He was president of the Bristol South District Medical Society from 1927 to 1928 and a councilor at the time of his death. He was a member of the House of Delegates of the American Medical Association in 1929. In that same year he was awarded a gold medal in the Scientific Exhibit of that Association for an exhibit showing experimental demonstration of the mechanism of transportation of abdominal viscera following rupture of the diaphragm. He was director of the Truesdale Hospital, which he had founded. He was a member of the founders' group of the American Board of Surgery and a member of the American Surgical Association, New England Surgical Society and the American Association for Thoracic Surgery. He was a fellow of the American College of Surgeons.

His widow, three sons and four daughters survive.

MEDICOLEGAL ABSTRACT

Right of Compensation: Proof of performance of Christian Science practitioner's services. In a recent Vermont case a Christian Science practitioner encountered some difficulty in proving that he had actually performed services for which the plaintiff was claiming compensation. The practitioner was not himself the plaintiff, the suit being brought by the person to whom he had assigned his claim. It appeared that it is a violation of the rules of the Church for a Christian Science practitioner to bring a suit at law to recover for treatments given to a patient.

To the Court it seemed the jury could have found that "the nature of the treatments with which we are here concerned is such that the defendant could have no way of knowing whether they were in fact given him, except what Haskins [the practitioner] stated about that matter. The treatments can be given to a patient when absent as well as when present." The Court stated:

> Haskins is the only one who knows whether he did in fact give the treatments in question. Neither the defendant nor anyone else can have any knowledge of this matter except what Haskins states about it. While he testified that he gave the treatments in accordance with the tenets of his church, yet, when asked to explain just what he did in giving such treatment, his answers were evasive, several not responsive and several were contradictory. Repeated efforts by the defendant's counsel failed to get any clear cut or definite statement as to just what he did in the giving of such treatment except that such treatment was some form of prayer. Neither could it be learned from him how long such treatments took or just when he claimed he gave them. Such uncorroborated testimony is not of a character to compel a verdict for the plaintiff. . . ."

The Court's opinion makes it perfectly clear that the decision is not to be construed as denying the right of a Christian Science practitioner to recover for treatments actually given. It does not go so far even as holding that the evidence required the jury to find against the practitioner, but goes only so far as holding that the jury was reasonable in doing so. The opinion, however, may possibly be interpreted as holding that a jury is always free to disbelieve the testimony of the practitioner that he gave the treatments unless it is corroborated by the testimony of someone else to the same effect. And if this is the correct interpretation, the claim of a practitioner for compensation for treatments given when neither the patient nor anyone else was present is a somewhat precarious claim. — (*Kennedy* v. *Williams*, 114 Vt. 54, 39 Atl. 2nd 193 [1944].)

CORRESPONDENCE

DIETS

To the Editor: It is 11 p.m., my four young ones are in bed, and my husband at the hospital, so I have finally had a minute to pick up the *Journal*, which came this noon, and, praises be, I finally have an answer for the people who disapprove of the way we feed our children. My husband has said ever since we had the first that accepted child-feeding is full of "pedigreed bunk," but try to convince a mother or a neighbor who thinks that you are not feeding your babies "scientifically"! I feel like framing your editorial "The Case against Fried Foods." It was only today that I thought of writing a medical magazine to ask, What *is* the difference between fish fried in fat and fish broiled with fat brushed on it? Our children have eaten from the family table from a very early age, to the horror of most beholders, and they are a fine healthy crew. However, since many well-meaning interferers prefer quoted authority to the evidence of their eyes, I am delighted to have something to quote. Thank you for easing the life of a harassed and busy mother. Now if I could only convince my mother that a small piece of home-made fruit cake is no worse for a child than, say, a slice of raisin bread, a few nuts and a piece of plain cake, eaten separately at the same meal, I would be all set.

ALISON BARSTOW MATHEWS
(Mrs. Frank P. Mathews)

Vashon, Washington

* * *

The *Journal* always welcomes any criticism of its editorial policies, particularly if the criticism is couched in terms of praise. We, too, have our vanities. Liberal as our policies are, however, even to the point of radicalism, we would not have our readers believe that we have entirely abandoned the idea of certain diets being suitable for children, and others, in a mild sense, for their parents. As Boswell said, "Claret is the liquor for boys, port for men; but he who aspires to be a hero must drink brandy." — ED.

BOOK REVIEWS

Trichinosis. By Sylvester E. Gould, M.D., D.Sc. 8°, cloth, 356 pp., with 128 illustrations. Springfield, Illinois: Charles C Thomas, 1945. $5.00.

This book is essentially a digest of the important publications on trichinosis from its earliest history to, and including, 1943. The subject matter is well organized, and the illustrations, most of which are photomicrographs, are excellent. Dr. Gould has produced the best monograph on trichinosis since that of Stäubli written in 1909.

Surgery of the Hand. By Sterling Bunnell, M.D. 4°, cloth, 734 pp., with 597 illustrations. Philadelphia: J. B. Lippincott Company, 1944. $12.00.

"Trauma involves all types of tissue, irrespective of the artificial divisions of our specialties. The surgeon must face the situation and equip himself to handle any and all of the tissues in a limb." This quotation from the preface underlies the high aim that the author has set himself in writing this excellent book, and it should be said that he has achieved his objective in a remarkable manner.

The book is divided into four parts. The first deals interestingly with the phylogeny and comparative anatomy of the hand and then proceeds to a discussion of the normal hand from the point of view of the skin, movements, mechanics of muscle and tendon, surgical anatomy, ossification and skeletal maturation. The second is a profitable account of the reconstruction of the hand, its examination, principles and operative technic as applied to problems of the skin and flexion contractures, bones, joints, nerves, tendons and muscles and concludes with a chapter on the arm in its relation to the hand. The third takes up in detail the question of injuries and infections and concludes with a vital discussion of the hand in industry. Finally, the fourth presents a succinct account of congenital deformities, vasomotor and trophic conditions and tumors of the hand.

This excellent book is particularly enhanced in its usefulness by the introduction of nearly six hundred beautiful illustrations. The references are timely and adequate, and one finds a good index. There is no doubt that every library will have this splendid book on its shelf, but it is urged that students, interns and surgeons purchase their own copies.

(*Notices on page xvii*)